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Differences in chest imaging between Omicron and non–Omicron coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis

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Abstract

Background Coronavirus disease 2019 (COVID-19) have posed a great threat to human health. We carried out this systematic review and meta-analysis for two objectives. First, to evaluate the differences in lung infection between the Omicron variants and the non-Omicron strains by chest computed tomography (CT); second, to evaluate the differences in chest CT features between COVID-19 patients with the Omicron variants and those with non-Omicron strains in CT-positive cases.

Methods We searched PubMed, Embase, Web of Science and China National Knowledge Infrastructure for articles and performed a meta-analysis using Stata 14.0 with a random effects model.

Results Our study included a total of 8126 patients with COVID-19, 4113 with the Omicron variants, and 4013 with non-Omicron strains. Patients with the Omicron variants were less likely to be CT-positive (OR = 0.14, 95% CI: 0.08–0.25), and further analysis among CT-positive patients was performed. Compared with the CT images of patients with non-Omicron strains, those of patients with the Omicron variants showed atypical pulmonary features (OR = 4.02, 95% CI: 2.31–6.98). Moreover, patients with the Omicron variants typically had lesions that were mainly located in the center of the lung (OR = 4.51, 95% CI: 1.38–14.76) and in a single lobe (OR = 1.72, 95% CI: 1.10–2.70). The patients with the Omicron variants were less likely to have lesions in both lungs (OR = 0.33, 95% CI: 0.15–0.69), more likely to have bronchial wall thickening (OR = 1.99, 95% CI: 1.05–3.77) and less likely to have the crazy-paving pattern (OR = 0.51, 95% CI: 0.33–0.81), linear opacity (OR = 0.26, 95% CI: 0.12–0.60), and vascular enlargement (OR = 0.54, 95% CI: 0.35–0.84).

Conclusions Through meta-analysis, which yields the highest level of evidence for evidence-based medicine, we further confirmed that there were significant differences in the distribution and manifestations of lesions between patients with non-Omicron strains and those with the Omicron variants on chest CT. The variation in SARS-CoV-2 has never stopped. Our findings are useful for the diagnosis and treatment of new SARS-CoV-2 variants that may appear in the future and provide a basis for public health decision-making.

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Keywords Omicron, Coronavirus disease 2019, Computed tomography, Systematic review, Meta-analysis

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a coronavirus with the natural capacity to undergo mutation and antigenic variation over time. The World Health Organization (WHO) has successively designated and confirmed the following five severe acute SARS-CoV-2 variants: Alpha, Beta, Gamma, Delta, and Omicron [1]. Omicron are the most mutated SARS-CoV-2 variants [2], which overtook other variants in terms of prevalence in just 9 weeks and quickly became the primary variants in the world [3]. Although the WHO announced the end of the COVID-19 public health emergency in May 2023 [4], COVID-19 will not disappear. There will likely be seasonal peaks similar to those of influenza in the future [5]. In July 2024, there were as many as 18,384 new cases of COVID-19 in Guangdong Province, China alone, all of which were Omicron variants [6].

Although real-time reverse transcription polymerase chain reaction (RT-PCR) is considered the gold standard test to determine confirmed cases, clinicians often recommend chest computed tomography (CT) scanning as a supplementary diagnostic test or a clinical triage if patients have severe symptoms that need immediate attention. Evaluating CT imaging features of COVID-19 has become crucial for effectively managing patients in clinical practice [7]. The Radiological Society of North America (RSNA) Expert Consensus Document classifies CT images of COVID-19 pneumonia into the following four categories: typical appearance, indeterminate appearance, atypical appearance, and negative for COVID-19 pneumonia [8]. Typical features of COVID-19 pneumonia include ground-glass opacities (GGOs) with or without consolidation in a peripheral, posterior, and diffuse or lower lung zone distribution and with a round appearance or a crazy paving pattern. Bronchial wall thickening and mucoid impactions, which are commonly seen in infections, are not typically observed; atypical features include bronchial wall thickening, central distribution, isolated lobar or segmental consolidation without GGOs, lung cavitation, and smooth interlobular septal thickening with pleural effusion [2, 8]. The emergence of Omicron changed the spread of the virus and the severity of the disease. When evaluating patients infected with COVID-19 pneumonia caused by Omicron using CT scans, radiologists should exercise caution when applying conventional criteria [9].

The conclusions of different studies are sometimes conflicting. For example, Zeng et al. [2] noted that CT-positive patients with non-Omicron strains presented more GGOs than those with the Omicron variants did, whereas Granata et al. [10] and Zhang et al. [11] did not find significant differences in the proportion of GGOs observed between the two groups of patients. Meta-analysis is a cornerstone of evidence-based medicine, which represents a systematic approach to clinical decision-making using high-quality evidence. We carried out this systematic review and meta-analysis for two purposes. First, to evaluate the differences in lung infection between the Omicron variants and the non-Omicron strains by chest CT; second, to evaluate the differences in chest CT features between COVID-19 patients with the Omicron variants and those with non-Omicron strains in CT-positive cases.

Materials and methods

This article was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Eligibility criteria

Our research included studies that met the following requirements: (1) chest images obtained via CT; (2) the article included an experimental group and a control group; and (3) the patients in the experimental group were all COVID-19 patients infected with the Omicron variants, and the patients in the control group were infected with one or more of the following strains of SARS-CoV-2: the original strain, Alpha, Beta, Gamma or Delta.

The exclusion criteria were as follows: (1) X-ray data, (2) case reports, (3) nonhuman studies, (4) data duplication, (5) reviews, comments, or abstracts, and (6) the sample size of the experimental group or control group was less than five.

Information source

We searched for articles published before August 20, 2024, in PubMed, Embase, Web of Science, and China National Knowledge Infrastructure. To collect as much data as possible, we did not limit the language of the articles and searched for topics in the title and abstract.

Search strategy

The search strategy was as follows: (Omicron[Title/Abstract]) AND ((((((Chest Images[Title/Abstract]) OR (Chest Image[Title/Abstract])) OR (CT[Title/Abstract])) OR (Computed Tomography[Title/Abstract])) OR (Radiology[Title/Abstract])) OR (Radiological[Title/Abstract]))

Study selection process

All articles retrieved from the database were imported into NoteExpress software, and duplicate articles were removed by matching titles, authors, and journals. We subsequently performed an initial screening of the articles by reading titles or abstracts. Articles that passed the initial screening were further screened by reading the full text to determine which articles were eligible for this meta-analysis.

Data selection process and items

Data extraction was performed by three authors to ensure accuracy. The first two authors independently screened the data, and disagreements were adjudicated by the third author.

The selected items included the total sample size, the number of COVID-19 patients with positive chest CT findings, CT image classification, and the distributions and manifestations of lesions shown by chest imaging. The distribution of lesions included peripheral, central, diffuse, and bilateral distributions, and the distribution of lesions in lobes. The manifestations of lesions included GGOs, consolidation, interlobular septal thickening, halo signs, reverse halo signs, lymphadenopathy, pleural effusion, bronchial wall thickening, crazy-paving patterns, air bronchogram, bronchiectasis, linear opacities, and vascular enlargement.

Study risk of bias assessment

The Newcastle–Ottawa quality assessment scale was used to assess the quality and risk of bias of the included articles. Each article had a perfect score of nine, and an article with a score of seven or more indicated that it was a low risk of bias and high quality.

Reporting bias assessment

Given that the number of included articles in our results was mostly less than 10, we did not use funnel plots. Instead, we employed Egger's test to evaluate reporting bias, with a p value > 0.05 indicating the absence of bias.

Statistical analysis

Since our results were all dichotomous variables, odds ratios (ORs) were used for data analysis and evaluation, and the confidence interval (CI) was set at 95%. The I^2 statistic was used to quantify heterogeneity and subgroup analysis was used to explore the source of heterogeneity: $I^2 \leq 50\%$ indicated low heterogeneity, $50 < I^2 \leq 75\%$ indicated moderate heterogeneity, and $I^2 > 75\%$ indicated high heterogeneity [12]. The statistical software used was Stata 14.0, and we used a random effects model to estimate the effect value. For each result, a p value of the z-test < 0.05 was considered statistically significant.

Results

Study selection

A total of 1796 articles were retrieved, including 353 from PubMed, 403 from Embase, 670 from the Web of Science, and 370 from the China National Knowledge Infrastructure. A total of 537 duplicate articles were removed using the duplicate identification function of NoteExpress software. Next, 831 and 316 irrelevant articles were excluded by reading the titles and abstracts, respectively. Among the remaining 110 articles, 92 were further excluded after the full texts were read. The detailed screening procedure is shown in Fig. 1.

Risk of bias in studies

The risk of bias in studies was assessed via the Newcastle–Ottawa quality assessment scale (Additional Table 1). We found that all studies included were of high quality and had a low risk of bias.

Characteristics and results of individual studies

All the SARS-CoV-2 infections in the studies were confirmed via RT-PCR, and COVID-19 pneumonia was distinguished on the basis of positive imaging findings of lung involvement. The samples in three studies were from patients with COVID-19 pneumonia [2, 10, 11], and the samples in the other 15 studies were from patients with SARS-CoV-2 infection [13–27]. In terms of strain type, the Omicron variants were examined in all the studies. Ten studies included the original strain [2, 11, 15–17, 19, 21, 22, 25, 26], six studies included the Alpha variant [10, 14, 18, 21, 22, 27], two studies included the Beta variant [21, 22], one study included the Gamma variant [21], and 11 studies included the Delta variant [10, 13, 16, 18, 20–24, 26, 27]. Except for three studies [2, 19, 22], all the other studies reported the number of doctors who interpreted the chest CT scans and discussed the experience of these radiologists. All the studies included provided the criteria used for determining CT-positivity. In addition, the severity of symptoms, hospitalization, comorbidities, treatment protocols, and ages of the COVID-19 patients are listed in Table 1.

Results of syntheses

CT-positive

We included 15 studies [13–27] to analyze the differences in lung infection between Omicron and non-Omicron strains (Table 2). Patients with the Omicron variants were less likely to be CT-positive (OR = 0.14, 95% CI: 0.07–0.27, $I^2 = 94.9\%$, $p < 0.001$; Fig. 2). Subgroup analysis revealed that non-Omicron strains contained one strain (OR = 0.15, 95% CI: 0.05–0.44, $I^2 = 94.7\%$, $p < 0.001$; Fig. 2) or multiple strains (OR = 0.13, 95% CI: 0.05–0.30, $I^2 = 93.7\%$, $p < 0.001$; Fig. 2), and the differences were all statistically significant.

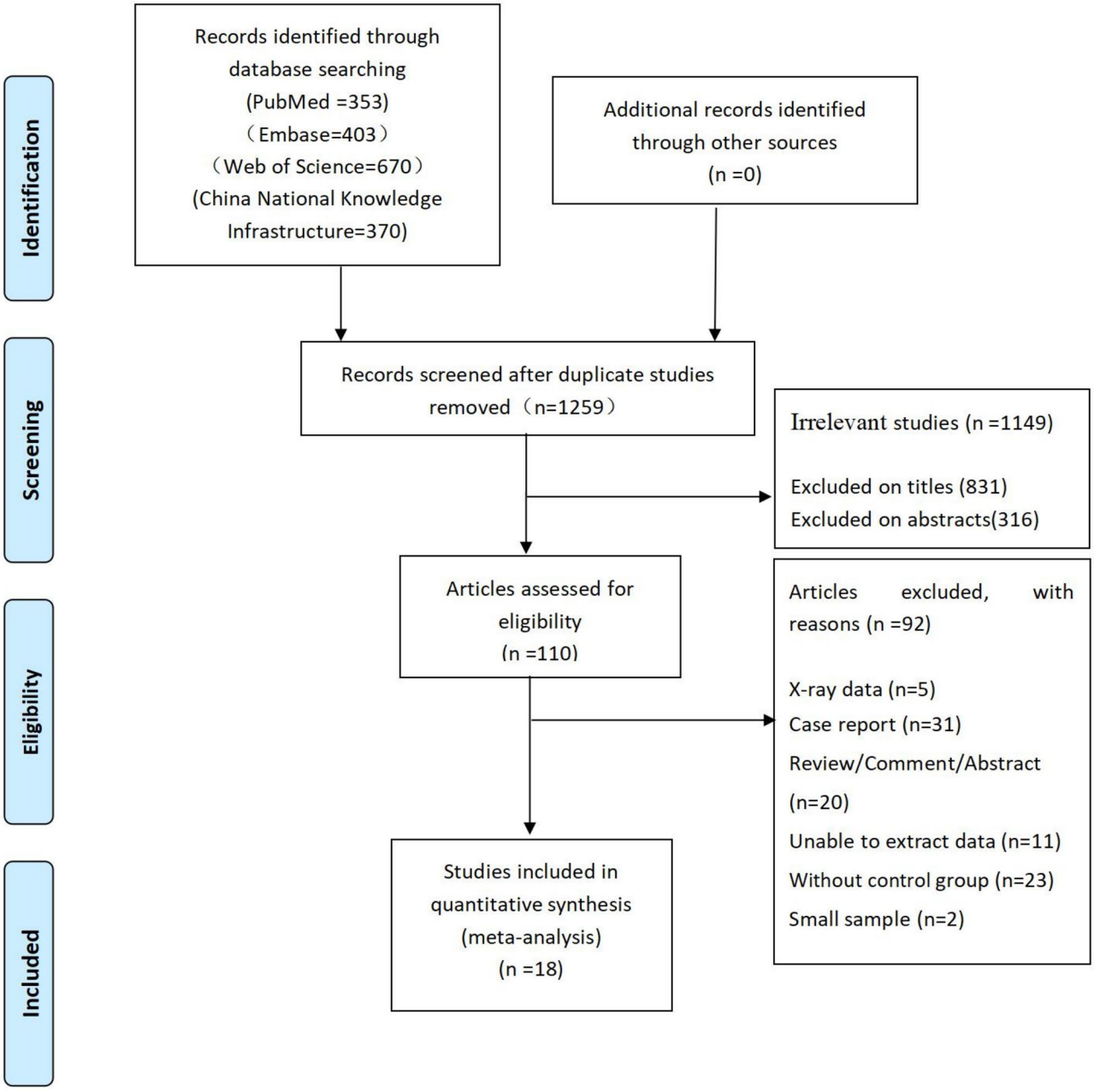

Fig. 1 Flow diagram of the article selection process

CT image classification

We further studied the differences in the imaging characteristics among CT-positive patients (Table 3) and found that, compared with the chest CT images of patients with non-Omicron variants, those of patients with the Omicron variants showed atypical pulmonary features (OR = 4.02, 95% CI: 2.31–6.98, $I^2 = 0.0\%$, $p < 0.001$; Additional Fig. 1), with fewer having typical pulmonary features (OR = 0.28, 95% CI: 0.13–0.60, $I^2 = 71.0\%$, $p = 0.001$; Additional Fig. 2). There was no significant difference in indeterminate pulmonary appearance between the two groups (OR = 1.96, 95% CI: 0.93–4.12, $I^2 = 64.1\%$, $p = 0.076$; Additional Fig. 3).

Distributions of lesions

Among CT-positive patients, we compared the distribution of lung lesions on chest images between Omicron patients and non-Omicron patients in three ways (Additional Table 2): (1) Omicron patients had lesions more centrally located in the lung (OR = 4.51, 95% CI: 1.38–14.76, $I^2 = 0.0\%$, $p = 0.013$; Fig. 3); there were no significant differences in the distribution of lesions in diffuse

Table 1 Characteristics of individual studies

a

Author	Publication year	Region	Study design	Patients		Types of non-Omicron strains
				Omicron	non-Omicron	
Zeng et al. [2]	2023	China	Retrospective	78	62	Original strain
Granata et al. [10]	2022	Italy	Retrospective	33	58	Alpha and Delta
Zhang et al. [11]	2024	China	Retrospective	69	96	Original strain
Yoon et al. [13]	2023	Korea	Retrospective	88	88	Delta
Yang et al. [14]	2022	China	Retrospective	374	38	Alpha
Lin et al. [15]	2023	China	Retrospective	37	31	Original strain
Han et al. [16]	2023	China	Retrospective	168	335	Original strain and Delta
Kirca et al. [17]	2022	Turkey	Retrospective	16	960	Original strain
Ito et al. [18]	2022	Japan	Retrospective	231	87	Alpha and Delta
Gu et al. [19]	2022	China	Retrospective	109	87	Original strain
Askani et al. [20]	2022	Germany	Retrospective	17	43	Delta
Nagaoka et al. [21]	2023	Japan	Prospective	48	137	Original strain, Alpha, Beta, Gamma and Delta
Liu et al. [22]	2023	China	Retrospective	119	313	Original strain, Alpha, Beta and Delta
Crombe et al. [23]	2023	France	Retrospective	1629	1080	Delta
Tsakok et al. [24]	2023	United Kingdom	Retrospective	40	66	Delta
Wang et al. [25]	2023	China	Retrospective	416	128	Original strain
Liu et al. [26]	2023	China	Retrospective	562	205	Original strain and Delta
Trinh et al. [27]	2024	Vietnam	Retrospective	79	199	Alpha and Delta

b

Author	The number of doctors who interpreted chest CT scans	The experience of doctors who interpreted chest CT scans	Criteria used for CT-positivity	Detection method of SARS-CoV-2
Zeng et al. [2]	2	The CT scans were independently evaluated by two board-certified thoracic radiologists (17 and 10 years of clinical experience in thoracic imaging, respectively).	According to the RSNA Expert Consensus Document, CT-positive images were classified into the following three categories: typical appearance, indeterminate appearance, and atypical appearance.	RT-PCR
Granata et al. [10]	2	Two radiologists with more than 10 years of thoracic-imaging analysis experience evaluated the severity of images. Another, more experienced, radiologist resolved any disagreement between the two radiologists.	The patients who had COVID-19 pulmonary involvement on CT images.	RT-PCR
Zhang et al. [11]	2	All images were reviewed and assessed by two cardiothoracic radiologists with more than 10 years of experience.	According to the RSNA Expert Consensus Document, CT-positive images were classified into the following three categories: typical appearance, indeterminate appearance, and atypical appearance.	RT-PCR
Yoon et al. [13]	2	Two experienced radiologists with more than 5 years of experience reviewed all CT images.	The COVID-19 patients who had viral pneumonia on pulmonary CT images	RT-PCR
Yang et al. [14]	3	All CT scans were reviewed independently by two cardiothoracic radiologists. In cases of disagreement between the two radiologic interpretations, the fellow-ship-trained cardiothoracic radiologist with 5 years of experience adjudicated a final decision.	Chest CT examination for patients with positive findings	RT-PCR

Table 1 (continued)

b

Author	The number of doctors who interpreted chest CT scans	The experience of doctors who interpreted chest CT scans	Criteria used for CT-positivity	Detection method of SARS-CoV-2
Lin et al. [15]	2	The CT images were reviewed by two radiologists (HSS, a senior thoracic radiologist with 30 years of experience, and YQF, an attending radiologist with 19 years of experience in interpreting chest CT images).	According to the RSNA Expert Consensus Document, CT-positive images were classified into the following three categories: typical appearance, indeterminate appearance, and atypical appearance.	RT-PCR
Han et al. [16]	NA	The CT results were evaluated by experienced CT radiologists.	All the patients had COVID-19 pneumonia (CT-positivity).	RT-PCR
Kirca et al. [17]	2	The chest CT images were evaluated by two specialist radiologists.	According to the RSNA Expert Consensus Document, CT-positive images were classified into the following three categories: typical appearance, indeterminate appearance, and atypical appearance.	RT-PCR
Ito et al. [18]	3	Three pulmonologists separately evaluated predominant distribution and morphologic patterns.	The patients who had COVID-19 pneumonia on CT images.	RT-PCR
Gu et al. [19]	NA	NA	COVID-19 patients with lung opacities in chest CT.	RT-PCR
Askani et al. [20]	2	The chest CT images were evaluated by two independent readers (PA, 8 years of experience and EA, 3 years of experience).	According to the RSNA Expert Consensus Document, CT-positive images were classified into the following three categories: typical appearance, indeterminate appearance, and atypical appearance.	RT-PCR
Nagaoka et al. [21]	2	Two experienced pulmonary radiologists with > 19 years of experience reviewed the chest CT scans.	Inflammatory lesion was detected by chest CT.	RT-PCR
Liu et al. [22]	NA	NA	The distribution or morphology of lesions were present on chest CT.	RT-PCR
Crombe et al. [23]	More than ten	The CT scans were interpreted by trained radiologists.	The involvement of lung parenchyma was showed on CT images.	RT-PCR
Tsakok et al. [24]	6	Five doctors had 2 year, 4 years, 5 years, 15 years and 20 years of thoracic imaging experience respectively, and another radiologist was receiving radiology training.	According to the RSNA Expert Consensus Document, CT-positive images were classified into the following three categories: typical appearance, indeterminate appearance, and atypical appearance.	RT-PCR
Wang et al. [25]	3	CT images were analyzed independently by two doctors with more than 5 years experience in chest imaging diagnosis, and one radiologist with more than 15 years experience resolved any disagreement.	COVID-19 patients with inflammatory lesion on chest imaging.	RT-PCR
Liu et al. [26]	3	Two radiologists with deputy senior title or above independently reviewed CT images, and the third radiologist with senior title would judge if there was disagreement.	The patients who had COVID-19 pulmonary involvement on CT images.	RT-PCR
Trinh et al. [27]	4	Three experienced radiologists read and reviewed individual chest CT images. In cases of disagreement, a fourth expert with more than 20 years of expertise would make the final decision.	The COVID-19 patients who had lung injury on CT images.	RT-PCR

c

Author	Severity of patients' symptoms	Inpatient or outpatient status	Treatment protocols	Age	Comorbidities
Zeng et al. [2]	NA	inpatient	NA	There was no difference in age between Omicron patients and non-Omicron patients.	There was no significant difference in comorbidities between Omicron patients and non-Omicron patients.

Table 1 (continued)

c

Author	Severity of patients' symptoms	Inpatient or outpatient status	Treatment protocols	Age	Comorbidities
Granata et al. [10]	NA	inpatient	NA	Omicron patients were older than non-Omicron patients.	NA
Zhang et al. [11]	There were more asymptomatic type in Omicron patients.	inpatient	NA	Omicron patients were older than non-Omicron patients.	There was no significant difference in comorbidities between Omicron patients and non-Omicron patients.
Yoon et al. [13]	NA	inpatient	NA	NA	NA
Yang et al. [14]	NA	inpatient	NA	Omicron patients were older than non-Omicron patients.	NA
Lin et al. [15]	The clinical severity of Omicron patients was significantly milder than that of non-Omicron patients, and there were fewer ICU admissions and lower mortality.	inpatient	Non-Omicron patients need more oxygen therapy, endotracheal intubation, antiviral therapy, antibiotic therapy, hormone, intravenoush and immunoglobulin than Omicron patients.	Omicron patients were younger than non-Omicron patients.	Omicron patients had less comorbidities than non-Omicron patients.
Han et al. [16]	There was no significant difference in moderate type, severe type and critical type between Omicron patients and non-Omicron patients.	NA	NA	There was no difference in age between Omicron patients and non-Omicron patients.	There was no significant difference in comorbidities between Omicron patients and non-Omicron patients.
Kirca et al. [17]	NA	NA	NA	There was no difference in age between Omicron patients and non-Omicron patients.	NA
Ito et al. [18]	NA	NA	NA	There was no difference in age between Omicron patients and non-Omicron patients.	Omicron patients had more comorbidities than non-Omicron patients.
Gu et al. [19]	Non-Omicron patients had more severe type than Omicron patients.	inpatient	NA	Omicron patients were younger than non-Omicron patients.	There was no significant difference in comorbidities between Omicron patients and non-Omicron patients.
Askani et al. [20]	NA	inpatient	There was no significant difference in oxygen therapy and intensive therapy between non-Omicron patients and Omicron patients.	There was no difference in age between Omicron patients and non-Omicron patients.	There was no significant difference in comorbidities between Omicron patients and non-Omicron patients.
Nagaoka et al. [21]	There was no significant difference in mortality between Omicron patients and non-Omicron patients.	inpatient	There was no significant difference in intermittent positive pressure ventilation and nasal high flow between non-Omicron patients and Omicron patients.	Omicron patients were older than non-Omicron patients.	Omicron patients had more comorbidities than non-Omicron patients.
Liu et al. [22]	There were more asymptomatic type in Omicron patients and more mild/ordinary type and moderate/severe type in non-Omicron patients.	inpatient	NA	There was no difference in age between Omicron patients and non-Omicron patients.	Omicron patients had more comorbidities than non-Omicron patients.
Crombe et al. [23]	NA	NA	NA	NA	NA

Table 1 (continued)

c

Author	Severity of patients' symptoms	Inpatient or outpatient status	Treatment protocols	Age	Comorbidities
Tsakok et al. [24]	Non-Omicron patients had more serious diseases and need more ICU admission.	inpatient	Non-Omicron patients need more noninvasive ventilation and high-flow oxygen administration than Omicron patients.	There was no difference in age between Omicron patients and non-Omicron patients.	There was no significant difference in comorbidities between Omicron patients and non-Omicron patients.
Wang et al. [25]	NA	inpatient	NA	Omicron patients were younger than non-Omicron patients.	NA
Liu et al. [26]	There were more mild type in Omicron patients and more severe/critical type in non-Omicron patients.	NA	NA	NA	NA
Trinh et al. [27]	NA	inpatient	NA	NA	NA

(OR = 1.21, 95% CI: 0.44–3.33, I^2 = 75.9%, p = 0.706; Fig. 3) and peripheral (OR = 0.67, 95% CI: 0.30–1.50, I^2 = 69.4%, p = 0.336; Fig. 3) forms between the two groups; (2) compared with non-Omicron patients, bilateral lesions were less common in the Omicron patients (OR = 0.33, 95% CI: 0.15–0.69, I^2 = 53.2%, p = 0.003; Additional Fig. 4); (3) we also compared the distribution of lesions in a single lobe and multiple lobes between Omicron and non-Omicron patients, and found that Omicron patients had more lesions distributed in a single lobe (OR = 1.72, 95% CI: 1.10–2.70, I^2 = 11.1%, p = 0.017; Additional Fig. 5).

Manifestations of lesions

The manifestations of the lesions are detailed in Additional Table 3. On chest images of CT-positive patients, Omicron patients presented more bronchial wall thickening (OR = 1.99, 95% CI: 1.05–3.77, I^2 = 21.0%, p = 0.035; Fig. 4), whereas crazy-paving pattern (OR = 0.51, 95% CI: 0.33–0.81, I^2 = 37.2%, p = 0.004; Fig. 4), linear opacity (OR = 0.26, 95% CI: 0.12–0.60, I^2 = 50.0%, p < 0.001; Fig. 4) and vascular enlargement (OR = 0.54, 95% CI: 0.35–0.84, I^2 = 0.0%, p = 0.006; Fig. 4) were rarely observed. Although Omicron patients had fewer GGOs than non–Omicron patients, the difference was not statistically significant (OR = 0.68, 95% CI: 0.42–1.09; I^2 = 56.3%, p = 0.110; Additional Fig. 6). There was no significant difference between the two groups in consolidation (OR = 1.10, 95% CI: 0.64–1.88, I^2 = 75.5%, p = 0.740; Additional Fig. 7), reverse halo sign (OR = 0.90, 95% CI: 0.20–4.02, I^2 = 34.1%, p = 0.893; Additional Fig. 8), lymphadenopathy (OR = 0.76, 95% CI: 0.28–2.01, I^2 = 49.9%, p = 0.575; Additional Fig. 9), interlobular septal thickening (OR = 1.03, 95% CI: 0.28–3.77, I^2 = 71.0%, p = 0.960; Additional Fig. 10), pleural effusion (OR = 1.19, 95% CI: 0.47–3.03, I^2 = 71.0%, p = 0.717; Additional Fig. 11), halo sign (OR = 1.15, 95% CI: 0.13–10.01, I^2 = 74.6%, p = 0.900; Additional Fig. 12), air bronchogram (OR = 0.40, 95% CI: 0.02–6.79, I^2 = 71.2%, p = 0.529; Additional Fig. 13), and bronchiectasis (OR = 1.75, 95% CI: 0.80–3.82, I^2 = 0.0%, p = 0.158; Additional Fig. 14).

Reporting biases

Egger's test was used for reporting bias analysis, and none of the results were found to have reporting bias (Additional Figs. 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38 and 39).

Heterogeneity

In our study, most results showed good heterogeneity, and only three showed high heterogeneity. Because the result in Fig. 3B included only four articles, we did not analyze them in subgroups. For the other two outcomes, we performed a subgroup analysis by using countries, type of strains in non-Omicron patients, and number of strains in non-Omicron patients, but the exact source

Table 2 Differences in lung infection between the Omicron variants and the non-Omicron strains

Author	Omicron patients		non-Omicron patients	
	Number	CT-positivity	Number	CT-positivity
Yoon et al. [13]	88	66	88	71
Yang et al. [14]	374	5	38	33
Lin et al. [15]	37	11	31	10
Han et al. [16]	168	73	335	308
Kirca et al. [17]	16	12	960	589
Ito et al. [18]	231	79	87	67
Gu et al. [19]	109	20	87	80
Askani et al. [20]	17	11	43	38
Nagaoka et al. [21]	48	16	137	76
Liu et al. [22]	119	37	313	287
Crombe et al. [23]	1629	1151	1080	945
Tsakok et al. [24]	40	25	66	56
Wang et al. [25]	416	134	128	123
Liu et al. [26]	562	63	205	149
Trinh et al. [27]	79	36	199	124

of heterogeneity was not found (Fig. 2 and Additional Figs. 15, 16, 17, 18 and 19).

Discussion

To the best of our knowledge, our study is the first systematic review and meta-analysis to compare the differences in chest CT features between patients infected with the Omicron variants and those infected with non-Omicron strains in detail. The main reason the Omicron variants have become the most prevalent SARS-CoV-2 variants is its high infectivity. Angiotensin-converting enzyme 2 (ACE2), the only experimentally confirmed SARS-CoV-2 receptor, can facilitate the entry of viruses into cells, and its expression level is considered a marker of susceptibility to COVID-19 [28]. The Omicron variants require less energy to engage with ACE2 than the Delta variant, which means that the Omicron variants are more vulnerable to ACE2 attachment than the Delta variant [29]. In addition, the horde of >50 mutations atone for the exalted binding capacity of the Omicron variants to ACE2 receptor and increased splitting of host furin at the spike protein, which further increases the infectivity and transmissibility of these variants [30].

In our study, non-Omicron samples containing one or multiple strains showed more lung infections than Omicron samples. A study by the University of Hong Kong found that the Omicron variants infect human bronchi more than 70 times faster than the Alpha variant and have a higher replication speed. In contrast, the original strain infects the lung more than 10 times faster than the Omicron variants, and the replication speed is also faster than the latter [31]. Hui et al. found that the Omicron variants were more sensitive to a cathepsin inhibitor but less dependent on transmembrane protease serine 2 (TMPRSS2) activity than the Delta variant. This implies that the Omicron variants enter cells mainly via the endocytic pathway, whereas the Delta variant prefers to fuse at the cell surface. Using a widespread endocytic pathway, the Omicron variants can infect cells expressing ACE2 independently of the presence of TMPRSS2, thus potentially expanding the cellular spectrum for infection. According to single-cell sequencing data, cells coexpressing ACE2 and cathepsins are more common in the upper airway than cells coexpressing ACE2 and TMPRSS2, which may help explain why Omicron is more capable of self-replicating in the bronchi [32]. Studies have shown that, compared with lower respiratory symptoms such as cough and shortness of breath in patients infected with non-Omicron strains, upper respiratory symptoms such as sore throat were more common in patients infected with the Omicron variants [14, 17]. Kontopodis et al. noted that the "NYNYLYRLF" peptide is an essential amino acid sequence in the RBM region (448–456 positions). This tyrosine (Y)-enriched peptide has 2 contact sites (Y449 and Y453) and is known as the NF9 peptide; in contrast to the Delta variant, the NF9 amino acid content of the Omicron variants remains unchanged, indicating that the NF9 peptide may lead to early activation of the immune system and the release of efficient cytokines, resulting in a faster immunological response and a reduction in SARS-CoV-2 pathogenicity [33]. The inability of the Omicron variants to effectively inhibit the interferon immune response of host cells may also lead to a reduced severity of infection [34]. Interferons are a group of proteins released by infected cells that signal to other system cells to resist the growth of viruses; this is a critical mechanism in fighting the replication of many viruses, including SARS-CoV-2 [35]. Another reason for the lower prevalence of COVID-19 pneumonia in the Omicron wave may be vaccination. Vaccination has been shown to reduce the severity of pneumonia [36]. Although the ability of the Omicron variants to escape vaccine immunity is greater than that of non-Omicron strains, the vaccination rate of COVID-19 patients during the Omicron epidemic was significantly higher than in the previous period [37–39].

Our study revealed that atypical pulmonary findings, such as the reverse halo sign, lymphadenopathy and pleural effusion, could not be used as imaging indicators to distinguish between the two groups of patients. However, we also found that radiologists classified more chest CT images of CT-positive patients with the Omicron variants as having atypical pulmonary features, suggesting that although not all atypical radiological features were significantly different between patients with non–Omicron strains and patients with the Omicron variants, atypical pneumonia is still more common in CT-positive patients with the Omicron variants.

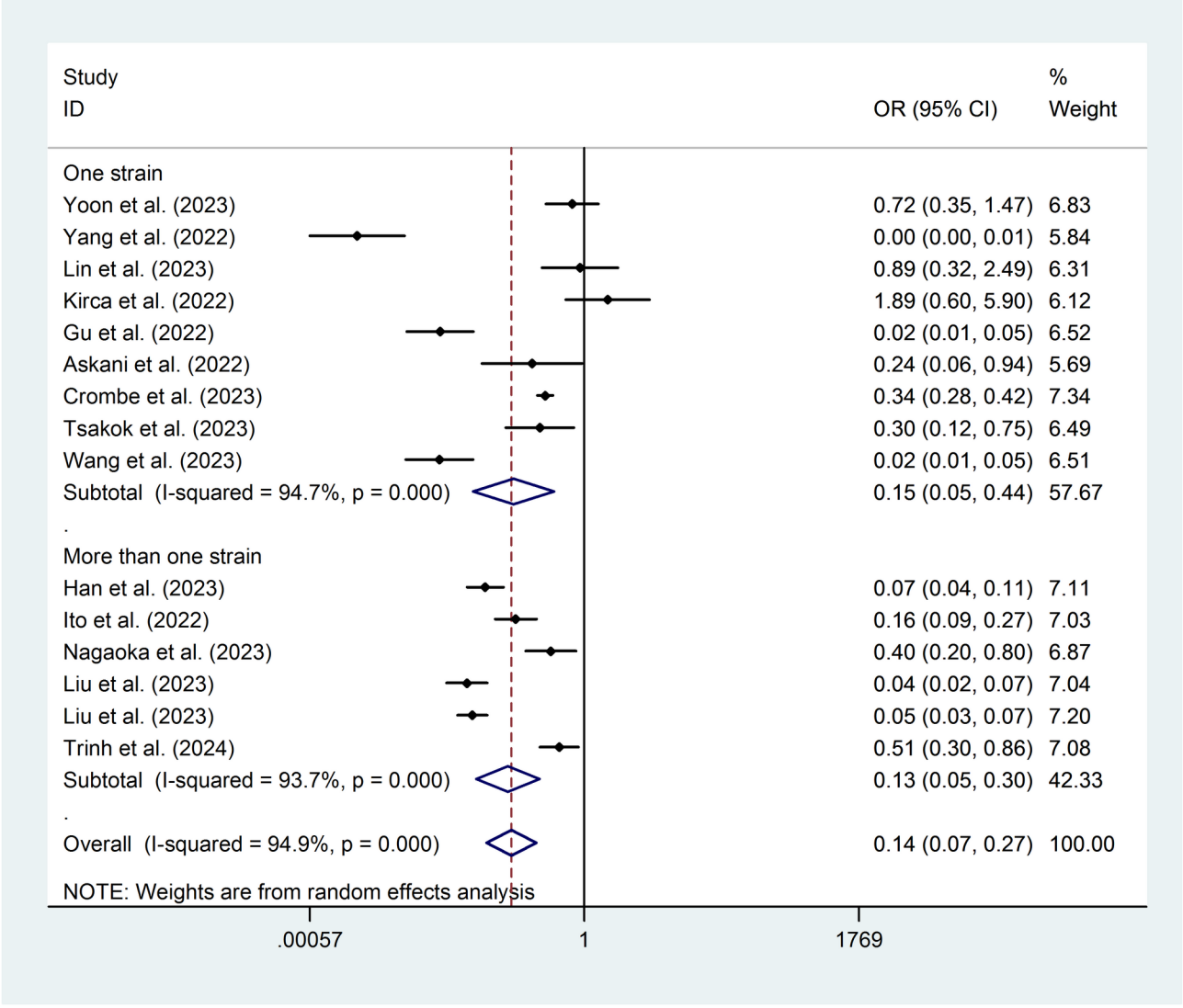

Fig. 2 Forest plot of differences in lung infection between the Omicron variants and the non-Omicron strains

Table 3 CT image classification among CT-positive patients

Author	Omicron				Non-Omicron			
	Number	Typical appearance	Indeterminate appearance	Atypical appearance	Number	Typical appearance	Indeterminate appearance	Atypical appearance
Zhang et al. [11]	69	55	12	2	96	79	15	2
Yoon et al. [13]	66	28	27	11	71	50	18	3
Han et al. [16]	73	48	13	12	308	283	11	14
Kirca et al. [17]	12	7	2	3	589	392	164	33
Askani et al. [20]	11	2	5	4	38	25	9	5
Tsakok et al. [24]	25	16	NA	NA	56	55	NA	NA

We focused on the chest imaging features of CT-positive patients infected with the Omicron variants and those infected with non-Omicron strains. Our study revealed that lesions in non-Omicron patients were more commonly observed in multiple lobes and more frequently involved bilateral lungs. This suggests that, even in CT-positive patients, infection with non-Omicron strains would cause more extensive lung injury than infection with the Omicron variants.

We also found that lesions in Omicron patients were more centrally concentrated. This may be because non-Omicron strains form patchy GGOs through infection,

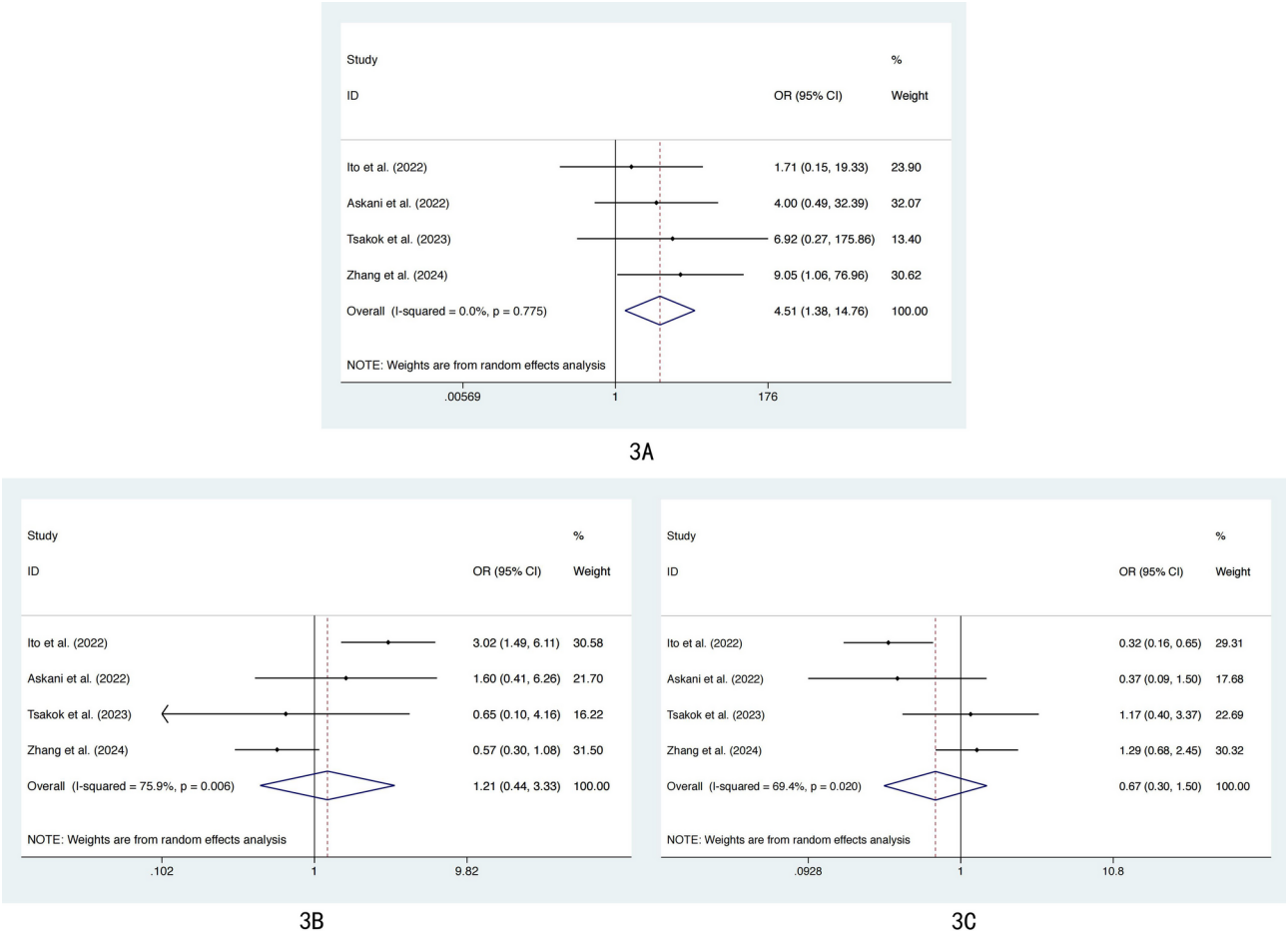

Fig. 3 Forest plot of differences in the distribution of lung lesions on chest images between Omicron and non-Omicron patients: (**A**) central, (**B**) diffuse, and (**C**) peripheral

and their main target cells are reportedly alveolar type II epithelial cells; however, there are relatively fewer alveoli in the central region of the lung [18]. GGOs are radiologic opacities that do not obscure the contours of close bronchovascular structures, indicating the presence of transudate or exudate in the alveoli. Still, the fluid amount is not large enough to create a stark contrast with the surrounding air spaces [40]. GGOs are commonly observed in the early stages of many inflammatory diseases, such as allergic pneumonia, viral infection, and mycoplasma infection [41]. After infection in the upper airway, owing to inefficient replication in the human lung [42], proliferation or invasion of the Omicron variants can be highly suppressed when the immune response or specific physiological defenses have been effectively induced. When a less effective immune response is induced after upper airway infection, proliferation or invasion of the Omicron variants in the lungs may be achieved, which mostly reflects pulmonary GGO lesions [21]. Although we found no significant difference in GGOs between Omicron and non-Omicron patients, the p value of 0.110 was close to the 0.05 cutoff. The results may change significantly if a meta-analysis is included in new studies.

Bronchial wall thickening is a marker of airway infection, and SARS-CoV-2 infection can lead to bronchial wall swelling [43]. Because the Omicron variants have an increased ability to infect the bronchus than non-Omicron strains, this may contribute to bronchial wall thickening being more common in patients infected with the Omicron variants. Our study revealed that, in CT-positive patients, the chest images of Omicron patients presented less crazy-paving pattern, linear opacity, and vascular enlargement. Crazy-paving is often used in imaging because its appearance resembles a path made of concrete fragments. This term was initially a pathognomonic sign in patients diagnosed with pulmonary alveolar proteinosis [44]. The pathophysiology of crazy-paving in COVID-19 is similar to that of Middle East respiratory syndrome and severe acute respiratory syndrome, which involve the pulmonary alveolar airspace and interstitial networks [45]. It starts with host cell entry of the virus into alveolar epithelial cells after inhalation via the upper respiratory pathway. The viral spike protein

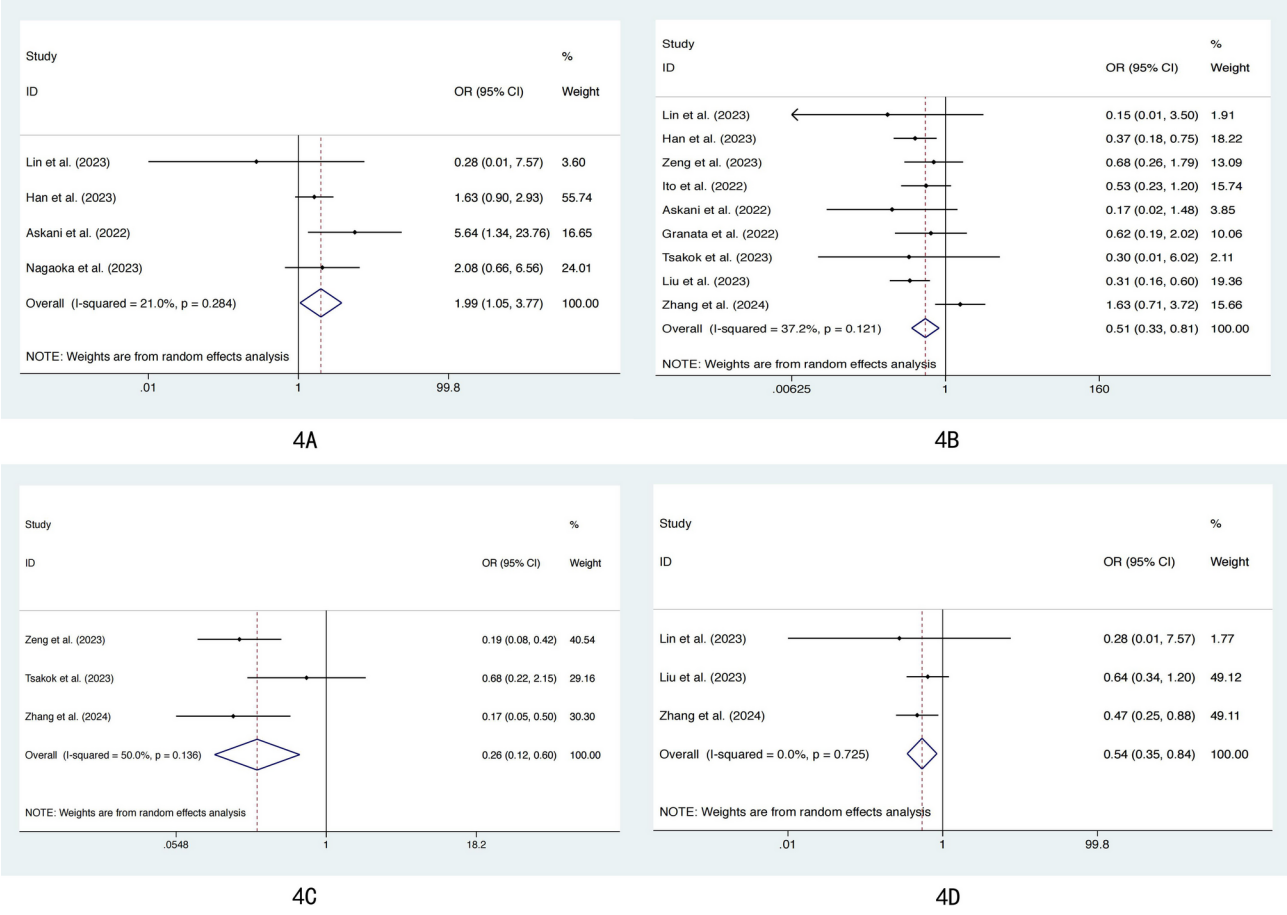

Fig. 4 Forest plot of differences in the manifestations of lung lesions on chest images between Omicron and non-Omicron patients: (**A**) bronchial wall thickening, (**B**) crazy-paving pattern, (**C**) linear opacity, and (**D**) vascular enlargement

attaches to ACE2 and transmembrane serine protease 2 [45, 46]. Once the host macrophage recognizes this antigen, a downstream cascade occurs, leading to excessive activation of proinflammatory cytokines, referred to as a storm. This cytokine storm leads to a hyperinflammatory response, leading to acute lung injury and respiratory failure [47]. Linear opacity and vascular augmentation are related to the clinical severity of COVID-19 patients, and these CT features are more easily observed in severe cases of COVID-19 [47, 48]. The linear opacity of COVID-19 patients may be caused by subsegmental atelectasis or secondary organizing pneumonia [49]. A study by Bai et al. revealed that vascular thickening was more common in patients with COVID-19 pneumonia than in those with non-COVID-19 pneumonia, considered one of the most distinguishing features of COVID-19 [50]. The vascular enlargement of COVID-19 patients may be attributed to a combination of coronavirus-induced direct cytopathic effects and virus-triggered host immune reactions, accompanied by a massive accumulation of proinflammatory factors in the lung characterized by endothelial injury and increased permeability [51].

The variation in SARS-CoV-2 has never stopped. Studying the differences in chest imaging findings between Omicron and non-Omicron patients is useful for the diagnosis and treatment of new SARS-CoV-2 variants that may appear in the future. Understanding the differences in the CT features of different strains is helpful for distinguishing between different types of infection more accurately and improving the accuracy of diagnosis. Different strains may cause different lung diseases. Clarifying these differences is helpful for formulating more targeted treatment plans and improving the prognosis of patients. Distinguishing the type of infection associated with different strains by CT features is helpful for tracking the spread of the virus, thereby providing a basis for public health decision-making, aiding in the rational allocation of medical resources, and reducing pressure on the medical system.

Limitations

Our study had limitations: Most of our data came from retrospective research, and there might have been selection bias. The vaccination rate of Omicron patients is

often higher than that of non-Omicron patients. Still, in the articles we retrieved, we could not extract enough data from patients with the same vaccination status for meta-analysis, which may have had a certain impact on the comparison of the chest CT features of the two types of patients; the CT images were obtained from different hospitals, and the scanning parameters and image quality were different, which might have affected the interpretation of certain imaging details. Chest CT features differ between ICU and non-ICU patients, and some lung CT features, such pleural effusion, are more common in ICU patients. Among the articles we included, only the article by Granata et al. [10] revealed detailed information about ICU patients. Moreover, chest CT data for ICU patients was not reported in the other articles; thus, we could not conduct related studies.

Conclusions

Patients infected with non-Omicron strains presented more imaging changes on chest CT than those infected with the Omicron variants. Even among CT-positive patients, the distributions of lesions in the lungs of non-Omicron patients were more extensive, and the manifestations of lesions were more severe. These results suggested that non-Omicron strains had a stronger ability to infect the lungs and might have a worse impact on the prognosis of COVID-19 patients.

Abbreviations

CI	Confidence interval
COVID-19	Coronavirus disease 2019
CT	Computed tomography
GGOs	Ground-glass opacities
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RT-PCR	Reverse-transcriptase polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

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Author contributions

Conceptualization: Z.W. Data curation: Z.Z., Z.W. and Y.H. Methodology: Z.Z. and Y.H. Writing-original draft: Z.Z. and Y.H. Writing-review & editing: X.L. and Z.W. All authors read and approved the final manuscript.

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Data availability

All data relevant to the study are included in the article/additional material, further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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