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The prominent chest CT findings in Covid-19 patients: A systematic review and meta-analysis

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ABSTRACT

Background: Assessing the quality and manner of pulmonary involvement through imaging modalities seems to be useful in predicting the severity of Covid-19 and thus determining the best disease management approach.The present study summarized systematically the chest CT findings of patients suspected to Covid-19.

Methods:Data abstraction was independently performed by two un-blinded reviewers on structure collection forms without divergences in data collection. The manuscript databases including Medline, Web of knowledge, Google scholar, Scopus, and Cochrane were deeply searchedfor all eligible studies based on the considered keywords. The risk of bias for each study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and also according to QUADAS-2 tool.

Results: Overall, 22 studies (including 4052 patients, overall mean age of 48.19 years ranged 42 to 57 years, male/female of 2113/1939) were reviewed. The pooled prevalence rate of CT positivity was 89.5% (95%CI: 95.4% to 92.6%). The common CT findings in Covid-19 patients

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include GOO in 78.2%, interlobular septal thickening in 48.5%, air bronchogram pattern in 44.5%, consolidation in 37.4%, crazypaving in 21.9%, nodules in 12.1%, reticular pattern in 9.8%, and pleuraleffusion in 7.3%. Other patterns including bronchiectasis, cavitation, lymphadenopathy, or pericardial effusion were rarely seen.

Conclusion: Pulmonary involvement can be revealed by chest CT scanning in about 90% of patients and the most prominent CT findings include GOO, interlobular septal thickening, air bronchogram pattern, consolidation, and crazypaving.

INTRODUCTION

New pneumonia with unknown origin was diagnosed in December 2019 in Wuhan, China that subsequent investigations revealed coronavirus as main the cause of this pandemic (1-3). This new virus was named as the new coronavirus of two causes of acute respiratory syndrome or SARS-CoV-2 and therefore the disease caused by it was also named as COVID-19 by the World Health Organization (4). The virus is the seventh member of the corona family of RNA viruses with enolope, which is next to other viruses in the family such as SARS and MERS. The first cases of the virus were identified among aquaculture vendors in Wuhan, and finally the person-to-person transmission was confirmed at the same time (5-7). As the virus spread worldwide, pandemic counts were reported in China and then in all countries (9, 8).Therefore, immediately a large number of articles on clinical evidence and its cognitive epidemics were published (9-11). Accordingly, the diagnosis of COVID-19 was determined primarily by confirmation of coronavirus nucleic acid in swabs, sputum or respiratory secretions by RT-PCR.However, the use of diagnostic kits has been largely time consuming.In addition, false negatives were gradually reported. In this regard, imaging tools, especially CT scans, were used to diagnose the severity and stages of the disease and were especially used in assessing the severity of viral pneumonia (12, 13). In recent reports, between 70 and 80% of CT findings have been matched with clinical manifestations, and therefore CT has been mentioned as an important and practical tool in the diagnosis and progression of the disease (14).Accordingly, different manifestations of CT with the severity of progression of pneumonia due to it have been considered and thereafter, five stages of the disease were defined based on CT findings: in the ultra-early stage, ground-glass opacities or GGO can be seen singly or repeatedly along with GGO-coated nodules, abscess consolidations, and air-bronchogram markers; in the early stage, multiple cases of GGO, pathy consolidation, or a combination of GGO and increased interstitial septal thickness with interstitial edema, alveolar capillary congestion, and exudative fluid are seen in the air sacs; in rapid progression, exacerbation of inflammatory lesions is observed in the form of consolidating opacities with air-bronchogram, which gradually change in size and density;in the consolidation stage, their size and density decrease; and finally, in the dissipation stage, the lesions may become more numerous in number and extent, and only limited consolodative, reticular opacity, and intertubular septal thickness are observed (15).But the important point is that due to the similar pathogenesis of COVID-19 with other pneumonias from other members of the coronavirus family, the diagnosis of COVID-19 pneumonia could not be made solely on the basis of these findings, and in fact these findings for COVID-19 are not exclusive (16,17). But in

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general it should be acknowledged that in patients with a negative RT-PCR result, CT scan evaluation can be very useful (18,19).Pneumonia is the most common clinical finding of COVID-19 and CT scan still seems to have a high value in reflecting the severity of the disease. The present systematic review study summarized the radiographic findings of patients suspected to Covid-19.

MATERIALS AND METHODS

Study selection

The present systematic review and meta-analysis followed the guideline for the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA). Firstly, the main question of our studywere suggested based on the authors purposes as "What are the main CT-based manifestations and findings of Covid-19". In the next step, the manuscript databases including Medline, Web of knowledge, Google scholar, Scopus, and Cochrane were deeply searched by the two blinded investigators for all eligible studies based on the considered keywords including "Covid-19", "computed sonography", "ground-glass opacity", "consolidation", "gender", and "age". The inclusion criteria were considered to retrieve the studies: 1) the studies finally assessed were those evaluated the prevalence rate of each CT findings based on gender and age indices, 2) due to the potential effects of history of any pneumonia, those studies including such patients were all excluded, 3) The studies were restricted to English language, 4) the studies with unclear or irreproducible results were all excluded, 5) lack of access to the manuscripts full texts was also considered as the inclusion criteria unless the abstracts had enough data for our analysis, 6) case reports, case series and review papers were all excluded. As shown in the flow diagram of the study selection (Figure 1), 273 articles were initially collected by database searching. After removing 3 articles due to evidences of duplication, 270 records were primarily under-screened. Based on the titles and abstracts, 196 records were excluded and the remaining 74 citations were assessed for further eligibility. Of those, 52 were also excluded due to incompleteness of the data and contents. In final, 22 articles were eligible for the final analysis (20-41) (Table 1).

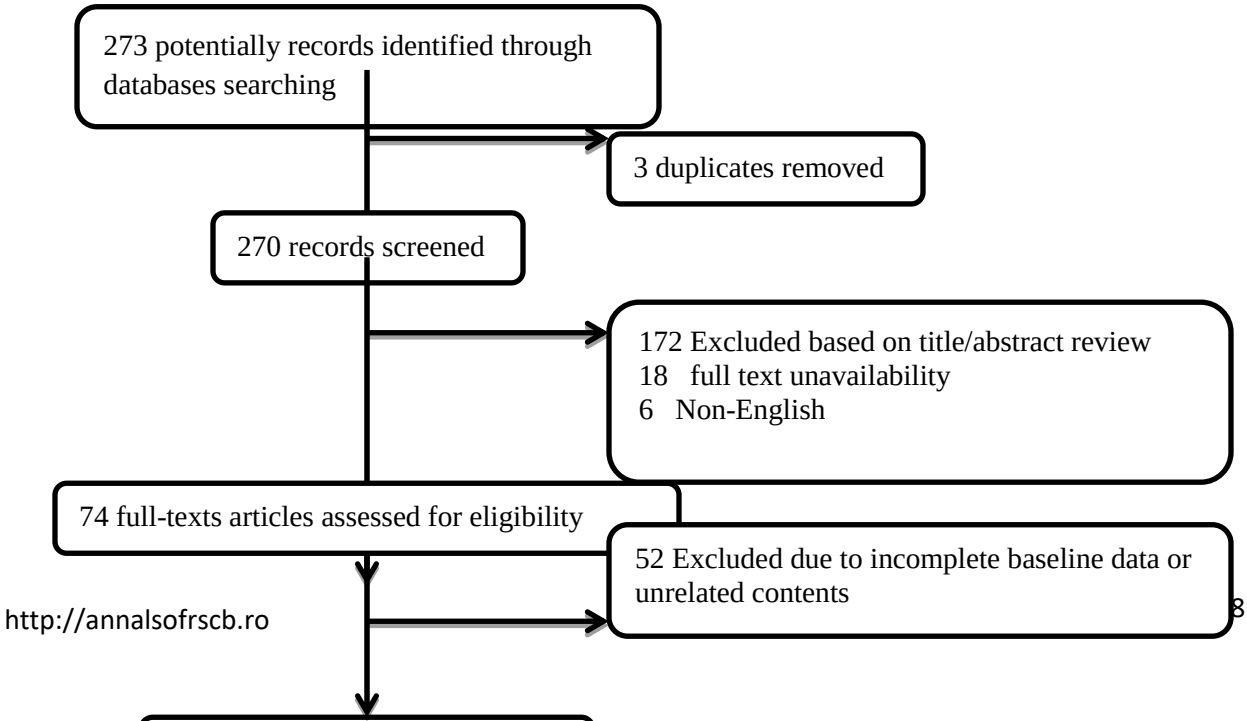

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Figure 1: The flowchart of screening the eligible studies

Table 1: Characteristics of reviewed studies

Author	Sample size	Mean age	Male/Female	Abnormal CT	CT findings
Ai (20)	1014	51.0	467/547	888	GGO, consolidation, interlobular septal thickening
Bernheim (21)	121	45.3	61/60	94	GGO, consolidation, crazy paving, pleural effusion, bronchiectasis, lymphadenopathy
Caruso (22)	158	57.0	83/75	102	GGO
Chen (23)	99	55.5	67/32	99	GGO
Chung (24)	21	51.0	13/8	18	GGO, consolidation, crazy Paving, reticular pattern
Dai (25)	234	44.6	136/98	219	GGO, vascular enhancement interlobular septal thickening, air bronchogram consolidation, fibrosis, air trapping
Ding (26)	112	55.8	51/61	102	GGO, crazy-paving pattern, consolidation and linear opacities, air bronchogram, bronchiectasis and pleural effusion
Guan (27)	1099	47.0	637/459	840	GGO, interlobular septal thickening
Han (28)	108	45.0	38/70	108	GGO, consolidation,

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					vascular wall thickening, crazy paving pattern, air bronchogram halo sign
Li (29)	83	45.5	44/39	83	GGO, consolidation, interlobular septal Thickening, crazy Paving, Reticular Pattern, nodules, pleural effusion
Liang (30)	88	42.7	51/37	84	GGO, consolidation, linear opacities, pulmonary nodules, Cavitation
Pan (31)	63	44.9	33/30	63	GGO, consolidation
Shang (32)	307	46.0	164/143	307	GGO, vascular enhancement sign, consolidation, fibrosis, air bronchogram, pleural thickening, Pleural effusion, lymphadenopathy

Table 1: (continued)

Author	Sample size	Mean age	Male/Female	Abnormal CT	CT findings
Shi (33)	81	49.5	42/39	81	GGO, consolidation, interlobular septal thickening, adjacent pleura thickening, air bronchogram, pleural effusion, bronchiectasis, lymphadenopathy
Song (34)	51	49.0	25/26	51	GGO, consolidation, peripheral, central, pleural effusion, pericardial effusion, lymphadenopathy

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Wang (35)	52	44.0	29/23	50	GGO, consolidation, interlobular septal thickening
Wang (36)	90	45.0	33/57	79	GGO, consolidation, pericardial effusion
Wu (37)	80	44	42/38	76	GGO, consolidation, interlobular septal thickening, crazy paving pattern, pleural effusion, pericardial effusion, lymphadenopathy
Xiong (38)	42	49.5	25/27	35	GGO, consolidation, interstitial thickening, fibrous strips, and air bronchograms,
Xu (39)	50	43.9	29/21	41	GGO, consolidation, interlobular septal thickening, air bronchogram, pleural effusion
Xu (40)	90	50.0	39/51	69	GGO,consolidation, crazy paving, interlobular septalthickening, airbronchogram, pleural effusion, pericardialeffusion, lymphadenopathy,
Yoon (41)	9	54.0	4/5	5	GGO,consolidation, crazy paving, airbronchogram,

Data abstraction and validity assessment

Data abstraction was independently performed by two un-blinded reviewers on structure collection forms without divergences in data collection. We resolved disagreements by consensus or by involving a third person. The study quality was evaluated based on the following criteria: 1) the systematic review and meta-analysis based on the questions primarily described and formulated; 2) inclusion and exclusion criteria predefined in the studies as eligibility criteria; 3) searching the literature performed on a systematic and comprehensive approach; 4) to minimize the bias, the full texts of the article were dually reviewed; 5) the quality of included studies were rated independently by the reviewers for appraising internal validity; 6) studies'

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characteristics and findings were comprehensively listed; 7) the publication and risk of bias were listed; and 8) heterogeneity was also assessed. The risk of bias for each study was assessed using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* and also according to QUADAS-2 tool. Any disagreement was resolved by discussion in the whole study team.

Statistical analysis

Dichotomous variables are reported as proportions and percentages. The pooled prevalence for each CT findings was assessed and presented by the odds ratio (OR) and 95% confidence interval (CI) as summary statistics. Cochran's Q test was used to determine the statistical heterogeneity. This test was complemented with the I^2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. Publication bias was assessed by the rank correlation test and also confirmed by the funnel plot analysis. Reported values were two-tailed, and hypothesis testing results were considered statistically significant at $p = 0.05$. Statistical analysis was performed using the Comprehensive Meta Analysis (CMA) software version 3.0 (Biostat, Englewood, NJ 07631 USA).

RESULTS

The present systematic review included the studies on adult patients suspecting Covid-19 referred to hospitals and medical centers to undergo CT scanning. In this regard, the studies focusing children or especial conditions (such as pregnancy) were not included in to our final analysis.According to our risk of bias assessment, all 22 studies yielded good quality and none of the citation was determined to have high risk of bias and therefore the pooled results should be persuasive (Figure 2). Overall, 22 studies (including 4052 patients, overall mean age of 48.19 years ranged 42 to 57 years, male/female of 2113/1939) were reviewed. The details of the patients' characteristics and main CT findings are presented in Table 1. As clearly shown, the positive CT involvement widely ranged from 56.0% to 100%. Hence, the pooled prevalence rate of CT positivity was 89.5% (95%CI: 95.4% to 92.6%). The heterogeneity across the studies in assessment of CT positivity for Covid-19 was significant ($I^2 = 88.340$, $p < 0.001$). As shown in Table 2 and Figure 3, the common CT findings in Covid-19 patients include GOO in 78.2% (95%CI: 69.8% to 84.7%), interlobular septal thickening in 48.5% (95%CI: 28.6% to 68.9%), air bronchogram pattern in 44.5% (95%CI: 30.5% to 59.5%), consolidation in 37.4% (95%CI: 27.8% to 48.1%),crazypaving in 21.9% (95%CI: 14.4% to 31.8%), nodules in 12.1% (95%CI: 2.8% to 39.7%), reticular pattern in 9.8% (95%CI: 1.5% to 43.7%), and pleuraleffusion in 7.3% (95%CI: 5.3% to 9.8%)(Figures 4A to 4H).The statistical heterogeneities between the studies in determining the prevalent imaging findings are fully relevant with an I^2ranged 44.271 to 98.091 ($P < 0.05$). The authors believed that the pointed heterogeneity was sourced from this fact that the judgment on imaging findings had not based on the severity of disease on admission or age of participants. Also, the moderate diagnostic value of CT scanning to definitive diagnosis of COVID-19 and its differentiating from other viral pneumonia should be also considered. Some

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studies also pointed other CT findings as the rare findings such as bronchiectasis (ranged 1.0 to 6.3%), cavitation (8.1%), and lymphadenopathy (1.0 to 6.0%). Interestingly, only a study by Han et al, vascular wall thickening was the prominent sign in CT revealed in 80.0% of patients that was not pointed in other studies.The Egger test detected a significant publication bias for all assessments.

Authors	Patient selection	Index test	Outcomes measurin	Flow and timing
Ai	+	+	+	+
Bernheim	+	+	?	+
Caruso	+	+		+
Chen	+	?		+
Chung	+	+	?	+
Dai	+	+	?	+
Ding	+	+	+	+
Guan	+	?	+	+
Han	+	+	+	+
Li	+	+	+	+
Liang	+	?	+	+
Pan	+	+	+	+
Shang	?	+	+	+
Shi	+	+	+	+
Song	+	?	+	+
Wang	+	+	+	+
Wang	?	+	+	+
Wu	+	+	+	+
Xiong	+	?	+	+
Xu	+	+	+	+
Xu	+	+	?	+
Yoon	+	+	?	+

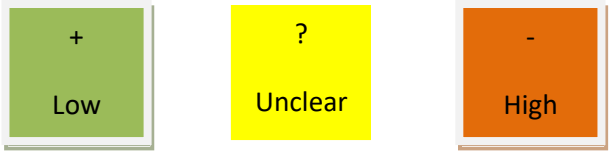

Figure 2: Assessment of the risk of bias

Table 2: Common CT findings in details

Author	GOO	Consolidati	Nodule	Air	Septal	Pleural	Crazy	Reticul

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		on		bronchogram	thickening	effusion	paving	ar pattern
Ai	409/888	447/888	24/888	---	8/888	---	---	8/888
Bernheim	41/94	2/94	---	---	---	1/94	6/94	---
Caruso	58/58	42/58	10/58	21/58	8/58	2/58	23.58	---
Chen	14/99	---	---	---	---	---	---	---
Chung	12/18	6/18	---	---	---	---	4/18	3/18
Dai	207/219	200/219	138/219	184/219	205/219	29/219	---	135/219
Ding	36/47	12/47	---	8/47	---	2/47	17/47	---
Guan	550/840	---	---	---	---	---	---	---
Han	65/108	6/108	---	52/108			43/108	---
Li	81/83	53/83	6/83	---	52/83	7/83	30/83	4/83
Liang	34/37	25/37	4/37	---	---	---	---	---
Pan	54/63	12/63	8/63	---	---	---	---	---
Shang	273/307	155/307	---	211/307	181/307	16/307	---	---
Shi	53/81	14/81	5/81	38/81	28/81	4/81	8/81	3/81
Song	39/51	28/51	---	41/51	38/51	4/51		11/51
Wang	48/50	19/50	---	17/50	---	---	---	---
Wang	49/79	18/79	---	---	---	6/79	---	---
Wu	73/76	50/76	---	---	47/76	5/76	23/76	---
Xiong	35/35	23/35	---	14/35	17/35	5/35	---	---
Xu	30/41	15/41	---	22/41	33/41	4/41	---	---
Xu	65/69	12/69	---	7/69	33/69	4/69	11/69	---
Yoon	35/77	2/40	---	16/77	---	---	4/40	---

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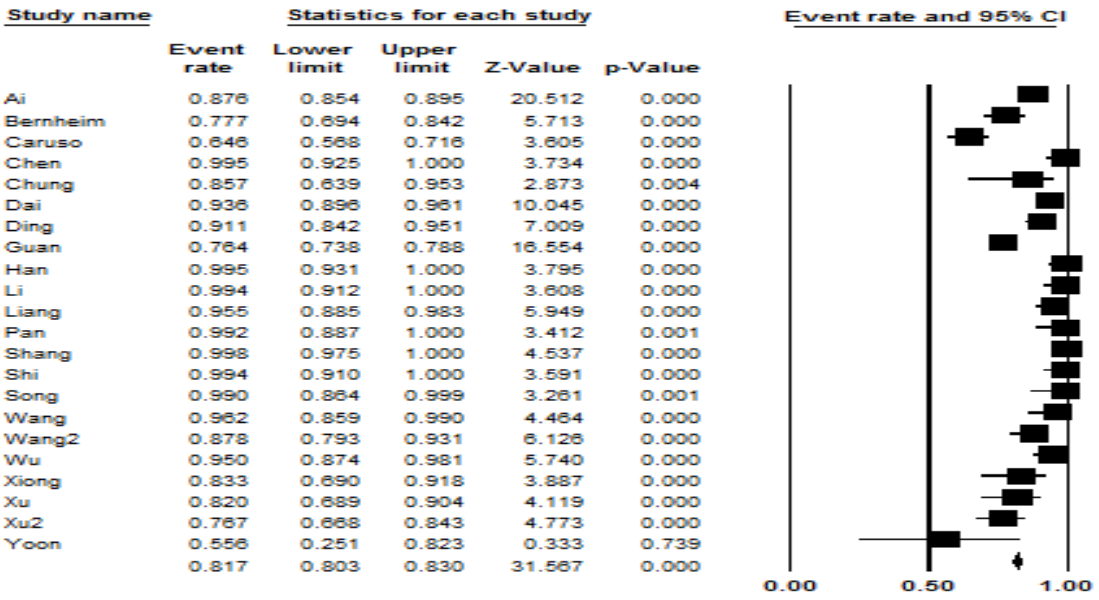

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Ai	0.876	0.854	0.895	20.512	0.000
Bernheim	0.777	0.694	0.842	5.713	0.000
Caruso	0.646	0.568	0.716	3.605	0.000
Chen	0.995	0.925	1.000	3.734	0.000
Chung	0.857	0.639	0.953	2.873	0.004
Dai	0.936	0.896	0.961	10.045	0.000
Ding	0.911	0.842	0.951	7.009	0.000
Guan	0.764	0.738	0.788	16.554	0.000
Han	0.995	0.931	1.000	3.795	0.000
Li	0.994	0.912	1.000	3.608	0.000
Liang	0.955	0.885	0.983	5.949	0.000
Pan	0.992	0.887	1.000	3.412	0.001
Shang	0.998	0.975	1.000	4.537	0.000
Shi	0.994	0.910	1.000	3.591	0.000
Song	0.990	0.864	0.999	3.261	0.001
Wang	0.962	0.859	0.990	4.464	0.000
Wang2	0.878	0.793	0.931	6.126	0.000
Wu	0.950	0.874	0.981	5.740	0.000
Xiong	0.833	0.690	0.918	3.887	0.000
Xu	0.820	0.689	0.904	4.119	0.000
Xu2	0.767	0.668	0.843	4.773	0.000
Yoon	0.556	0.251	0.823	0.333	0.739
	0.817	0.803	0.830	31.567	0.000

Figure 3: The pooled prevalence of CT positivity in patients suspected to Covid-19

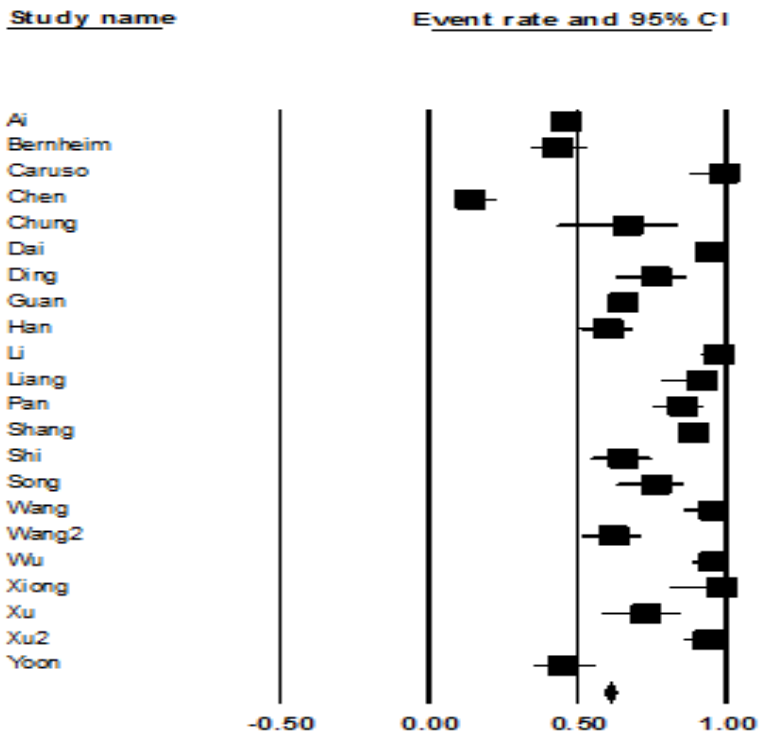

Figure 4A: the pooled prevalence of GOO as the CT finding inCovid-19 patients

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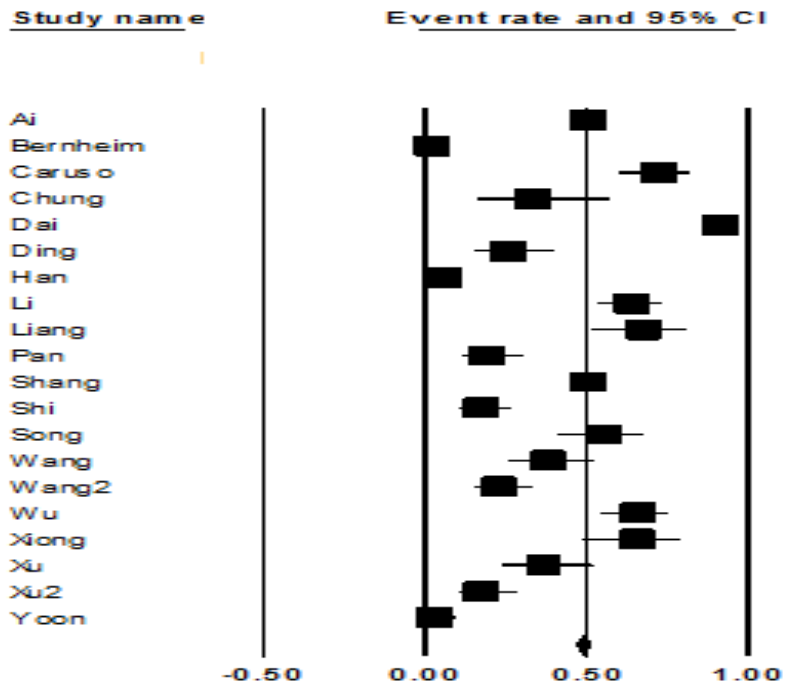

Figure 4B: the pooled prevalence of consolidation as the CT finding inCovid-19 patients

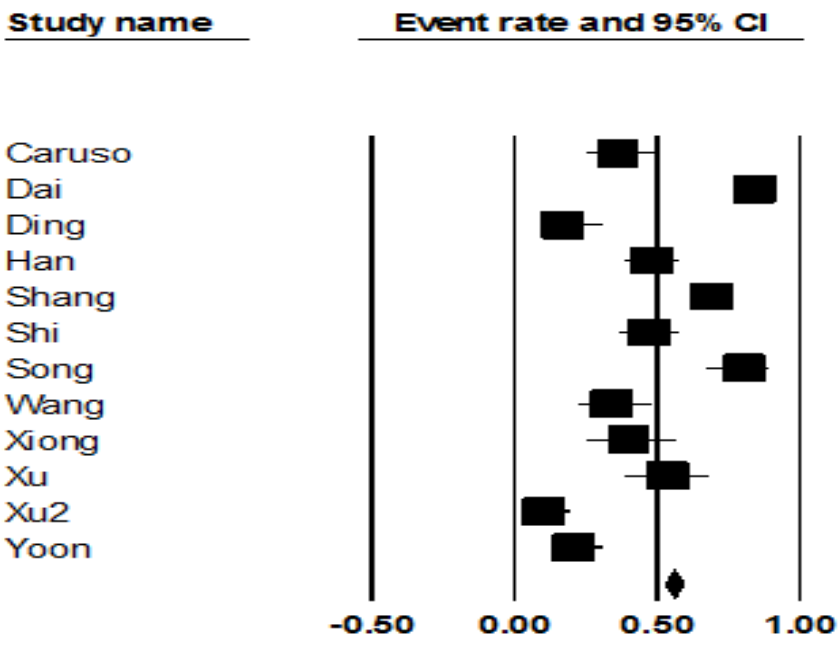

Figure 4C: the pooled prevalence of air bronchogram pattern as the CT finding in Covid-19

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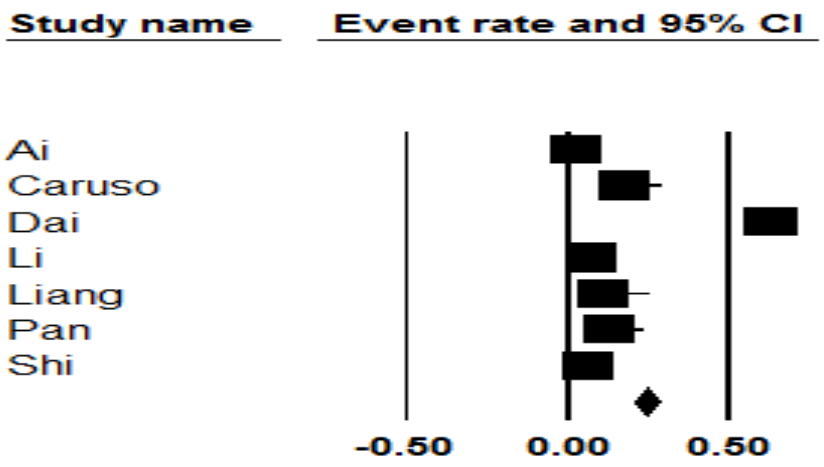

Figure 4D: the pooled prevalence of nodules as the CT finding in Covid-19

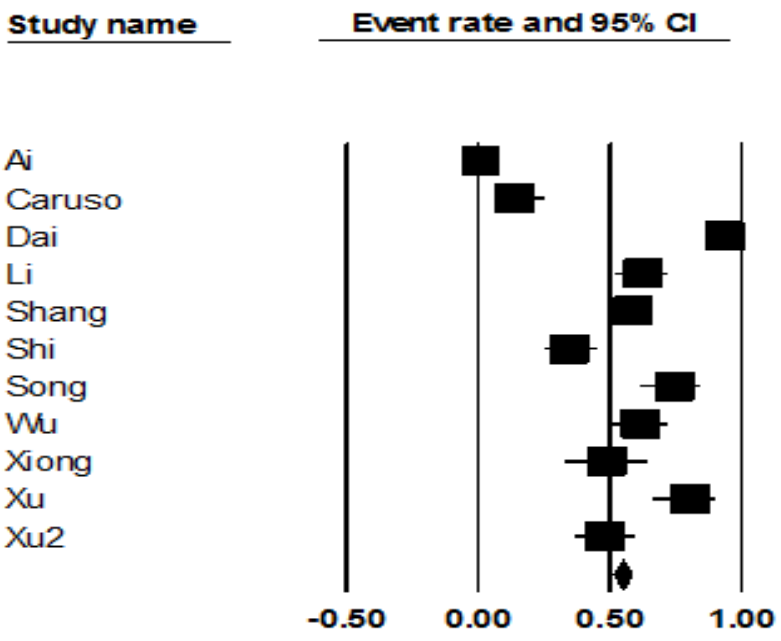

Figure 4E: the pooled prevalence of interlobular septal thickening as the CT finding in Covid-19

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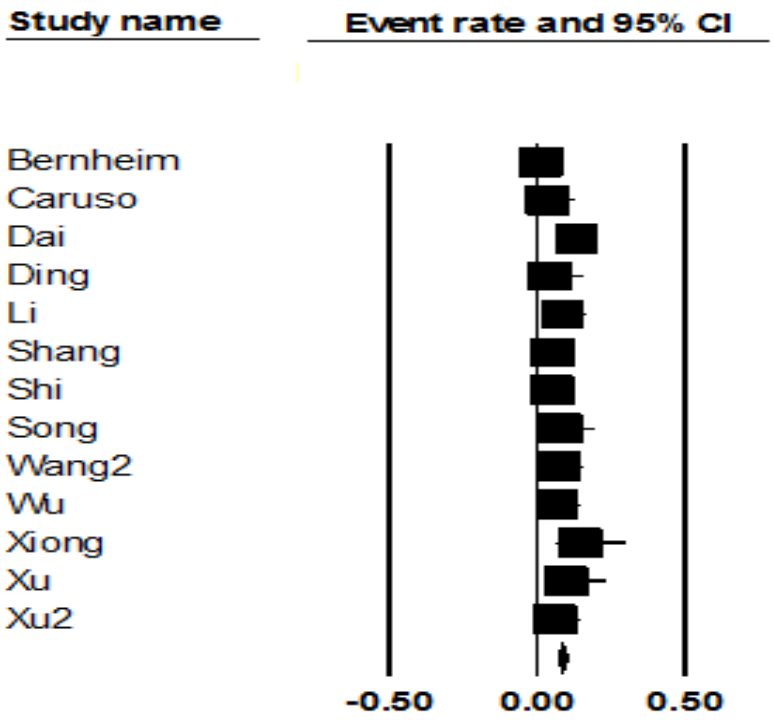

Figure 4F: the pooled prevalence of pleural effusion as the CT finding in Covid-19

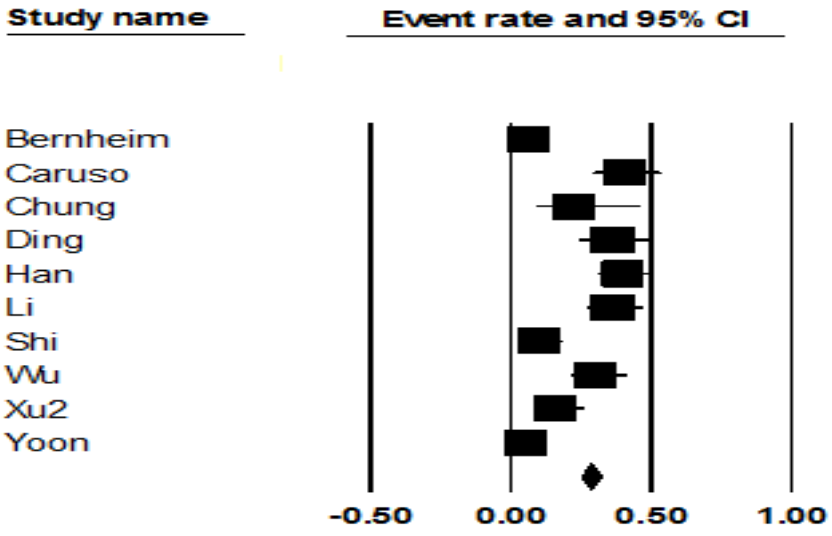

Figure 4G: the pooled prevalence of crazy paving as the CT finding in Covid-19

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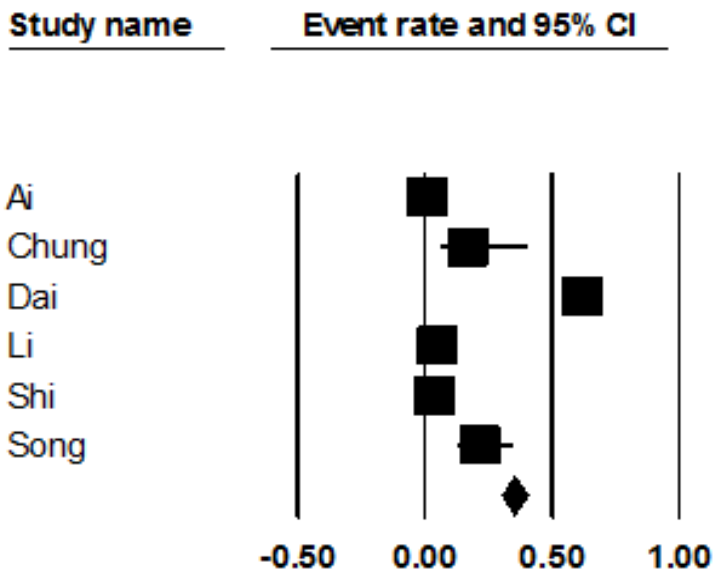

Figure 4H: the pooled prevalence of reticular pattern as the CT finding in Covid-19

DISCUSSION AND CONCLUSION

According to our systematic review, although assessment by CT scanning is the main managerial approach for assessing the presence and severity of pulmonary involvement due to Covid-19, this modality has a limited value so that according to our observation, in about 10% of patients with prominent clinical manifestations related o the disease, CT is completely clear and no evidence of Covid-19 pulmonary defects is detected. Also, a wide variation of pulmonary signs can be revealed in chest CT in Covid-19 patients. As shown in our meta-analysis, a significant heterogeneity has been found in the pooled prevalence of each of pulmonary signs related to Covid-19 indicating a mysterious and inhomogeneous face of pulmonary involvement of disease. For this reason, the basis of exclusive use of CT scan in the diagnosis of the disease is not possible, and in fact, a multifaceted approach including clinical manifestations, molecular diagnosis and sensitive imaging techniques to assess pulmonary involvement of the disease is necessary.According to the author's observations, in some patients with decreased arterial oxygen saturation, pulmonary involvement was not detectable and, conversely, in some patients in good general condition, in an incidental CT scan, extensive and bilateral pulmonary involvement was quite evident.These issues emphasize two important points. First, in estimating the risk of disease, a combination of clinical evidence and findings of pulmonary CT must be considered, and second, no definite and definable feature of pulmonary involvement can be presented to diagnose the disease or determine its severity. In this regard, studies have emphasized the importance of two findings of consolidation or crazy paving pattern to predict the severity of the disease (42,43), which, of course, has not been proven in other studies.But in general, what can be cited based on our findings is that the signs of GOO, interlobular septal thickening, air bronchogram pattern, consolidation, and crazypaving can be seen in a notable

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number of patients and other patterns such as protrusion of lung nodules, pleural or pericardial effusion, bronchiectasis, cavitation, lymphadenopathy, or reticular pattern may be found in a small number of patientsthat will definitely not be diagnostic for the disease.Although some sources cite the two findings of GOO and consolidation as typical manifestations of disease-related pulmonary defects (44,45), we do not believe so, and the emergence of pulmonary manifestations seems to depend on several factors.As mentioned earlier, the frequency of each of the pulmonary findings associated with the disease was associated with significant heterogeneity. This issue stems from several factors. First, the incidence of pulmonary findings appears to be entirely dependent on the age of the patients. Recent studies may have shown a marked difference in the pattern of pulmonary involvement in children and the elderly compared to other age subgroups (46,47), and none of the studies have evaluated the pattern of pulmonary involvement at different ages.Second, due to the high load of referrals to emergency departments and medical centers in countries with high epidemic disease, CT findings are interpreted by assistants with little experience in this regard, which greatly increases the chances of false negatives and the possibility of underestimation of pulmonary defects. On the other hand, considering the multiple behaviors of the virus in different communities (what has been clearly seen in the reported experiences), it seems that the severity of the disease and in fact the severity of pulmonary involvement are completely different in the communities.In fact, valuing CT findings in patient risk classification may be valuable in one community and insignificant in another.Therefore, in order to achieve reliable results and confirm the findings of the present review, studies with several characteristics including patient age groups, regional studies, determining disease severity at the time of referral, as well as the final interpretation of the findings by experienced experts is absolutely necessary and recommended.

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