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Derleme / Review

The Prevalence of Ground-Glass Opacity and Consolidation Symptoms of Covid-19 By Meta-Analysis

Covid 19 İçin Buzlu Cam Opasitesi ve Konsolidasyon Belirtileri Prevalansının Meta Analizi

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Özet

Bu çalışmada, bilgisayarlı göğüs tomografisinde en yaygın görüntüleme bulguları olan buzlu cam opasitesi (GGO) ve konsolidasyon sonuçları incelenerek daha kesin Covid-19 tespitini sağlamak için yayınlanan çalışmalardan elde edilen sonuçlar kullanılarak meta analiz yönteminin uygulanması amaçlanmıştır. Çalışmaya gerçek zamanlı polimeraz zincir reaksiyonu (rRT-PCR) pozitif vakaların görüntü özelliklerini bildiren ve SARS-Cov-2 enfeksiyonunu doğrulayan yayınlanmış hakemli makaleler dahil edilmiştir. Bu makalelerin çalışma türü vaka serisi, geriye dönük veya ileriye dönük kohort şeklindedir. Araştırma kapsamındaki çalışmalara, Covid-19, şiddetli akut solunum yolu sendromu corona virüsü 2 (SARS-Cov-2), bilgisayarlı göğüs tomografisi, konsolidasyon ve GGO anahtar kelimelerinin radyografik araştırma veri tabanı Secure Australia (RNSA), The Science Direct ve National Library of Medicine'de araştırılması ile ulaşılmıştır. Arama terimleri sonucunda üç veri tabanından toplam 310 makale toplandı ve makaleler tarandı. Buzlu cam opasitesi ve konsolidasyon bilgilerinin olmaması nedeniyle 250 makale çıkarıldı. Geriye kalan makalelerden, çalışma türü nedeniyle 24 makale, gün kriterini sağlamaması nedeniyle 7 makale, eksik ve yanlış veriler nedeniyle 9 makale çıkarıldı. Sonuçta 20 makale meta-analiz çalışmamıza dahil edildi. Bilgisayarlı göğüs tomografisi pozitif olan bulgularda, buzlu cam opasitesinin 5 güne kadar mevcut olduğu, beşinci ve sonraki günlerde konsolidasyona dönüştüğü görülmüştür. Analiz sonuçlarına göre; Covid-19'un erken evresi için buzlu cam opasitesinin prevalansı %82 ve konsolidasyonun prevalansı %40'tır.

Anahtar Kelimeler: Meta analiz, Covid-19, rRT-PCR test, bilgisayarlı göğüs tomografisi

Abstract

In this study, it was aimed to apply the meta-analysis method of the results obtained from the published studies to provide a more precise Covid-19 detection by examining the results of ground glass opacity (GGO) and consolidation, which are the most common imaging findings in chest computed tomography (CT). Published peer-reviewed articles reporting the image characteristics of real-time reverse transcription–polymerase chain reaction (rRT-PCR) positive cases and confirming Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) infection were included in the study. The study type of articles were case series, retrospective or prospective cohort studies. The studies under the scope of the research were reached from the National Library of Medicine, the research network for a Secure Australia (RNSA) and The Science Direct databases by searching the keywords Covid-19, SARS-Cov-2, computed chest tomography, Consolidation and GGO. As a result of the search terms, in total 310 articles were collected from three databases and articles were scanned, 250 articles were removed due to lack of GGO and Consolidation information, 24 studies were eliminated due to study type, 7 studies were unsuitable for day criteria, and 9 studies were eliminated due to missing and incorrect data. After all, 20 studies were included in our meta-analysis study. In the positive CT findings, it is known that the GGO is present for up to 5 days, the GGO turns into consolidation on the fifth and the following days, and according to the analysis result; for the early stage of Covid-19, the GGO Prevalence is 82% and Consolidation Prevalence is 40%.

Keywords: Meta-analysis, Covid-19, rRT-PCR test, chest computed tomography

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1. Introduction

Meta-analysis is a statistical analysis providing the presentation of the studies, conduction for the same purpose from a single source, determining the causes of inconsistency and heterogeneity between the studies and obtaining statistically more precise results from the studies conducted with small sample groups.(1) Meta-analysis is a quantitative statistical analysis of several separate but similar experiments or studies in order to test the pooled data for statistical significance. (2)

1.1.Weighting of Studies Participate in Meta Analysis by Fixed Effect and Random Effect Models

It is important to understand the two concepts when combining studies.

True Effect Size: It refers to the effect size in the population.

Observed Effect Size: It refers to the effect size of the added studies.

If the number of studies participating in the meta-analysis is too large, the "Observed Effect = True Effect" situation arises. The difference between the true effect and the observed effect is called sampling error.

Observed Effect of i-th study:

$$Y_i = \theta_i + \varepsilon_i \quad (1)$$

$$Y_i = Observed\ Effect \quad (2)$$

$$\theta_i = True\ Efect \quad (3)$$

$$\varepsilon_i = Sampling\ Error\ Between\ Studies \quad (4)$$

$\varepsilon_i \sim N(0, vi)$. Therefore the Yi's are assumed to be unbiased and normally distributed of their corresponding true effect. (3)

$$\theta_i = \mu + \zeta_i \quad \text{True Effect} \quad (5)$$

"ζ_i" shows the variability of effect size between studies and "ε_i" variability of sampling error within studies.

In condition $\zeta_i = 0$ then $\theta_i = \mu$ and $Y_i = \mu + \zeta_i + \varepsilon_i = \theta_i + \varepsilon_i = \mu + \varepsilon_i$ occurs. It means the observed effects size of studies and true effect size are equal.

The distance of observed effect size from the population mean (μ) is expressed by $\boldsymbol{\tau}$

(Standart deviation) and $\boldsymbol{\tau^2}$ = the population variance**,** the total amount of heterogeneity among the true effects. The variance value plays a role in the determination of the weights when calculating the population effect value.

$V_i = \varepsilon_i^2$ = The variance of Y_i. (The Sampling Variance) (6)

If the Population Variance is $\tau^2 = 0$ then the weight function should be

$$w_i = \frac{1}{Vi_{Yi}} \quad Fixed\ Effect\ Model. (3) \quad (7)$$

If the Population Variance is $\tau^2 \neq 0$ then the weight function should be

$$w_i = \frac{1}{Vi_{Yi} + \tau^2} \quad Random\ Effect\ Model. (3) \quad (8)$$

When calculating the effect size in the model, the random efect model or the fix effect occurs according to the presence or absence of the variance (τ^2) between the studies resulting from the real effect variability (ζ_i) of the studies. While analyzing studies in homogeneous structure, it should be calculated by fixed effect model; otherwise analyzing heterogeneous studies should be calculated by random effect model. The fixed or random effect model is highly determinative on the amount of population impact size.

Population effect size function is:

$$\mu = \frac{\sum_{i=1}^{k} w_i * Y_i}{\sum_{i=1}^{k} w_i} \quad (9)$$

$$V_M = \frac{1}{\sum_{i=1}^{k} w_i} \quad \text{Variance of Total Effect Size} \quad (10)$$

$$SE_M = \sqrt{V_M} \quad \text{Standard Error of Total Effect Size} \quad (11)$$

$\%\ 95\ CI = \mu \pm 1.96 * SE_M$ The Confidence Interval of Total Effect Size (12)

1.2.Calculating Prevalence with Meta Analysis

Calculating prevalence with meta-analysis methods is based on the inverse variance method (4,5)

$p_i = log\left(\frac{a/n}{1-a/n}\right)$ a=number of event and

n=number of observation (5)

Prevalence equation

$V_i = \varepsilon_i{}^2$ = The variance of p_i (The Sampling Variance). (14)

$w_i = \frac{1}{Vi_{pi}}$ The weight function for i'th study. (15)

Thus, the pooled prevalence estimate P, according to the inverse variance method, then becomes:

$P_{pooled} = \frac{\sum_{i=1}^{k} w_i * P_i}{\sum_{i=1}^{k} w_i}$ the pooled prevalence equation (4,6) (16)

$V_{(p)} = \frac{1}{\sum_{i=1}^{k} w_i}$ the variance of meta-analysis (17)

$SE(P) = \sqrt{V_{(p)}}$ the standard error (18)

$CI(P) = P \pm Z\alpha_{/2} SE(P)$ confidence interval (19)

$Z\alpha_{/2}$ denotes the appropriate factor from the standard normal distribution for the desired confidence percentage.

1.3.The Heterogeneity Test Cochran Q

Cochran's Q test is the traditional test for heterogeneity in meta-analyses, allows us to decide whether to combine the effect size into a single population.

The test hypotheses are:

$H_0: \theta_i = \theta_2 \ldots \ldots = \theta_k = 0$ or $H_0: \sigma_B^2 = 0$ (B=Between) $H_0: \sigma_W^2 = 0$ (w=within)

H_1: At least one variance differs.

Cochran Q test statistic is calculated as follows.

$Q = \sum_{i=1}^{k} W_i (Y_i - \mu)^2$ and (20)

$\mu = \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i}$ (13)(21)

If Q test value < χ^2 critical value, then we accept that H_0 hypothesis and meta-analysis effect size calculation type should be calculated with the homogeneity fixed effect model.

In December 2019, Covid-19 with agent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) occurred in Wuhan, a city of China, and spread all over the world.

According to the China Government's guide for the SAR-Cov-2 infection, the key indicator for hospitalization must be reverse transcription polymerase chain reaction (RT-PCR) or gene sequencing for respiratory or blood specimens (National Administration of Traditional Chinese Medicine). (7)

Viruses most commonly cause lung infections. Viral pneumonia images are different from other respiratory infections and inflammatory lung diseases. Viruses in the same viral family share a similar pathogenesis: therefore, CT imaging is important in the diagnosis of lung diseases for distinguishing patterns. (8)

The studies include images were analyzed for the following aspects: Presence of Ground-Glass Opacity (GGO): defined by increase in lung density but without covering the pulmonary blood vessels and bronchial walls; Presence of lung consolidation: defined by higher density than GGO and blurred margins of pulmonary blood vessels and bronchial tubes.

Limitation sample collection and kit performance the viruses may not be detected

in the upper respiratory samples, mostly 0-7 days after illness onset. Some severe cases viral ribonucleic acids (RNAs) could not be detected in the upper respiratory samples while positive in the bronchoalveolar lavage fluid. Except that, computed tomography (2) images of some cases showed typical viral pneumonia with GGO, whereas viral Ribonucleic Acid infections (RNAs) were not detected by throat swap samples. In this context, chest CT may provide benefit for diagnosis of Covid-19. (9)

Typical radiographic features of all Covid-19 patients included GGO and multifocal patchy consolidation. With RT-PCR results as reference, the sensitivity, specificity, accuracy of chest CT to diagnose Covid-19 infections were 97%, 25%, and 68%, respectively.(9) Another study's result for the sensitivity and specificity of chest CT with repeated RT-PCR was 95% and 35%. (10)

Incubation period of Covid-19 disease is 1 to 14 days, mostly three to seven days. General symptoms are fever, fatigue and dry cough.

In 0-2 days of symptoms onset, chest CT tends to be normal or Broncho vascular markings may start. *The early/initial stage* of the disease (0-4 days) shows the previously identified and best recognized features of Covid-19 infection, which consists of peripheral-based GGOs without subpleural sparing. *The progressive stage* of disease (5-8 days) shows an increasing amount of GGO relative to early stage. There can be vascular thickening and associated intralobular septal thickening "crazy paving pattern". *The peak stage* (10-13 days) includes consolidation and may include secondary complications of the disease. This step may include an even less specific pattern. The distinctive feature of *the absorption stage* (≥14 days) is the improvement of the aeration of the lungs with resolving features of "crazy paving", continuous solubility of GGO and parenchymal bands. In addition, there may be changes in fibrosis at this stage. (11)

In a suspected clinical case with typical clinical symptoms and previous exposure to individuals with SARS-Cov-2, a combination of chest CT imaging and RT-PCR assay may help to increase the Covid-19 diagnosis. For this reason, it is of crucial importance to define imaging patterns of Covid-19 pneumonia in order to diagnose the viral infection promptly in acute stages and to lead to the correct work-up. (12) Figure 1 shows the CT results of **A**: 28-year-old man who had a cough and fever for 3 days and **B**: 79-year-old male whose PCR test was positive.(28)

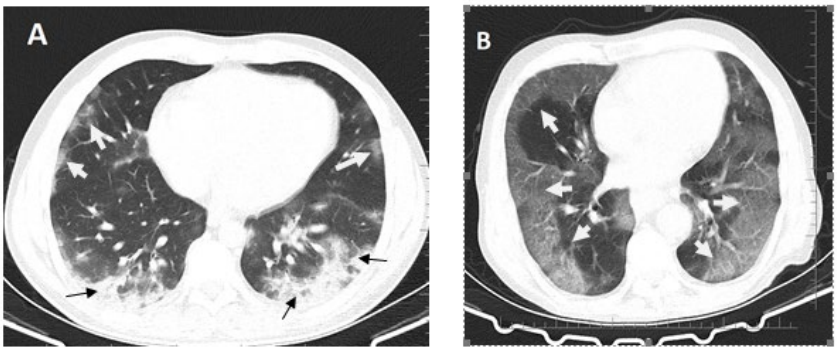

Figure 1. ***A****: 28-year-old male patient with complaints of nausea and vomiting for 10 days, fever and cough for the last three days.Non-contrast enhanced chest CT showed multiple peripheral patchy ground glass opacities in bilateral multiple lobular and subsegmental with obscure boundary (white arrows). In addition, areas of consolidation in the bilateral lower lobes were observed on the CT scan (black arrows).* ***B****: A 79-year-old male patient is admitted to the emergency room with fever and cough. The patient whose PCR test was positive, showed multiple peripheral patchy view glass opasities (white arrows) in the thorax CT examination. (28)*

Although rarely the RT-PCR negative patients had early stage (0-4 days) opacification, which is the most obvious lung finding of SARS-Cov-2, on chest CT imaging made us think about the importance of imaging for the diagnosis of Covid-19 disease. With the

progression of the disease, consolidation begins to form in the lungs. In order to contribute to the diagnosis and prognosis of Covid-19 disease, we considered it appropriate to investigate the prevalence of Consolidation and Opacification in 0-4 days which we call early stage.

In this meta-analysis, we aim to summarize the results from published studies quantitatively to provide a more precise detection Covid-19 by GGO and Consolidation which are the most common imaging findings on chest CT of patients, in other word we try to get the prevalence of related symptoms.

In this study, our question is what the consolidation and opacification rate is in the computed tomography within the first 4 days of hospitalization of disease whose Covid-19 rRT-PCR test positive and have symptom fever.

2. Material and Methods

2.1. Protocol and Registrations

The subject and method of our research were determined on 7-15 April 2020. Meta-analysis was the most appropriate method to answer our research question, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The purpose of the PRISMA Statement is to help the authors to develop their systematic review and meta-analysis reports. The critical evaluation of the research conducted by PRISMA, when it is compared to randomized studies, is clearer. However, the PRISMA checklist is not an assessment tool that can be used to measure the quality of the review. (13)

2.2. Eligibility Criteria

We included published peer-reviewed articles that reported image characteristics of rRT-PCR positive cases confirmed SARS-Cov-2 infection. Appropriate study designs to evaluate imaging characteristics are case control, retrospective or prospective cohort studies and case series. Article language limit was not set, we included publications from January 1, 2020 to May 25, 2020. Letters, opinion articles and studies that did not provide original data were excluded.

2.3. Information Sources And Search Strategy

The studies included in Meta-Analysis were taken from The National Library of Medicine (www.ncbi.nlm.nih.gov/pubmed), the publication of radiographic The Research Network for a Secure Australia (RNSA) (ww.pubs.rnsa.org) and The Science Direct (www.sciencedirect.com) databases. The publication related to Covid-19, SARS-Cov-2, chest CT, Consolidation and GGO were completely reviewed, these features were also search terms we used.

2.4. The Properties of Study Selection

The research criteria were clear and Covid-19 articles were open to share in databases, thus made literature review easier. Initial selection articles strategy was first screen by title and abstract. Limiting the research to three databases is a precaution to avoid bias. Any descriptive features that characterize the patients included in the study were not taken into account (age, smoking status etc.)

For this reason, articles which were studied with specific patient groups such as pediatric, pregnant, heart disease, kidney transplant were not included in the study. The articles in which numerical values were inconsistent and made by different people using the same data were excluded. Case Reports were not included in study, but the findings of these cases were compared with the results of the study. PRISMA method was used for the quality of the study. A total of 20 study met inclusion criteria. The PRISMA 2009 Flow Diagram is shown in Figure 2. (13)

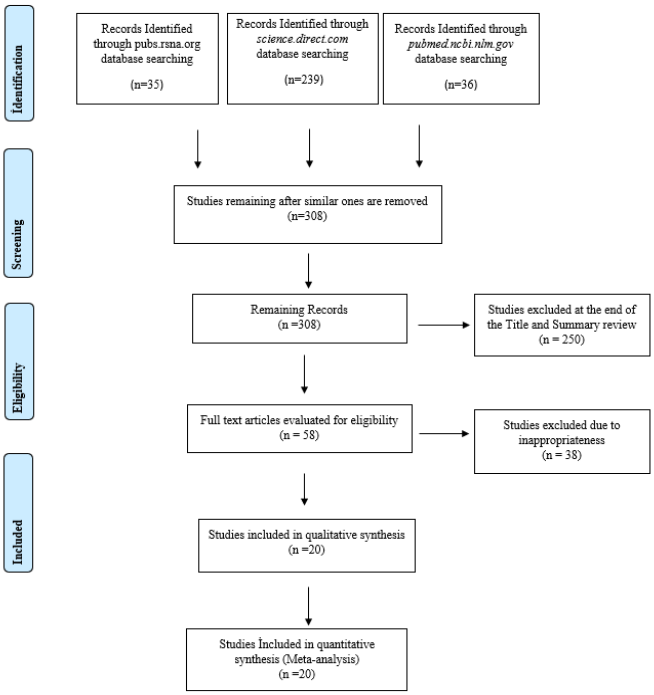

Figure 2. *PRISMA 2009 Follow Diagram*

2.5. Assessment of Methodological Quality and Risk of Bias

Calculation was made with the log values of the research findings and the confidence interval value of each study was given. Funnel plot and Egger's test were applied to investigate bias. Apart from three databases, any article was not included in the study and these databases were examined in detail for collecting data.

We used inverse variance method for counting the effect size of each study. The most used methods Mantel-Haenszel and One-step Peto's do not require to estimate the variance. For this reason, Mantel Haenszel only applies a fixed effect model. Also Peto's method only allows us to get odds ratio. (1) Statistical heterogeneity between studies was evaluated by Cochran's Q test, I2, H2, Tau2 indexes. For Q satatistic p< 0.100 was considered statistically significant for heterogeneity, I2>50%, H2 >1.15, for Tau2>0.130 (according to (14)) was considered to have moderate heterogeneity. For puplication bias, we conducted funnel pilot and it was checked by Edger's test that p<0.05 was considered statistically significant. For all statistical analysis used by R statistical software with package "meta" and "metafor" program.

3. Results

3.1 Study Selection and Characteristics

First, a total 310 articles were collected from three databases because of search terms. After screening those articles, 250 articles were excluded due to the lack of information of GGO and Consolidation. 24 studies were eliminated due to the study type (case record), 7 of them were eliminated due to the inappropriate day criterion and 9 of them were eliminated due to the missing and incorrect data. The design of the studies which were included in meta-analysis; 15 were retrospective studies, 2 were prospective studies and 3 were case series. Properties of studies which were included to the Meta-analysis for Prevalance of GGO is shown in Table 1. Properties of studies which were included to the Meta-analysis for Prevalence of Consolidation is shown in Table 2.

Table 1: Properties of studies which were included to the Meta Analysis for Prevalance of GGO

Study No	Authors	Ground Glass Opacities		Sample Size	CT Day	Study Design	Reference
		GGO+	GGO-	N			
1	Chung, M., et al.	19	2	21	on admission	Retrospective	(19)
2	Caruso, D., et al.	58	4	62	on admission	Prospective	(15)
3	Wang, Y., et al.	49	30	79	on admission	Prospective	(20)
4	Bai, H.X., et al.	200	56	256	on admission	Retrospective	(18)
5	Bernheim, A., et al.	45	24	69	on admission	Retrospective	(21)
6	Wang, K., et al.	80	34	114	on admission	Retrospective	(22)
7	Huang, L., et al.	6	2	8	on admission	Case Series	(23)
8	Luo, Z., et al.	9	3	12	on admission	Retrospective	(24)
9	Fang, X., et al.	11	3	14	on admission	Case Series	(25)
10	Peng, S., et al.	10	1	11	on admission	Case Series	(26)
11	Guan, C.S., et al.	47	6	53	on admission	Retrospective	(27)
12	Xu, X., et al.	65	25	90	on admission	Retrospective	(28)
13	Shi, H., et al.	31	5	36	on admission	Retrospective	(29)
14	Ding, X., et al.	36	11	47	on days 0. and 3.	Retrospective	(30)
15	Lomoro, P., et al.	40	2	42	on days 0. and 3.	Retrospective	(12)
16	Li, X., et al.,	106	25	131	on days 0. and 3.	Retrospective	(31)
17	Wang, X., et al.	863	149	1012	on days 0. and 4.	Retrospective	(32)
18	Zhou, Z., et al.	33	1	34	on days 0. and 4.	Retrospective	(33)
19	Nie, W., et al.	150	13	163	on days 0. and 4.	Retrospective	(34)
20	Liu, Z., et al.	59	13	72	on days 0. and 4.	Retrospective	(35)

Table 2. Properties of studies which were included to the Meta-analysis for Prevalence of Consolidation

Study No	Authors	Consolidation		Sample Size	CT Day	Study Design	Reference
		Cons+	Cons-	N			
1	Chung, M., et al.	6	15	21	on admission	Retrospective	(19)
2	Moher, D., et al.	42	20	62	on admission	Prospective	(15)
3	Wang, Y., et al.	18	61	79	on admission	Prospective	(20)
4	Bai, H.X., et al.	150	106	256	on admission	Retrospective	(18)
5	Bernheim, A., et al.	24	45	69	on admission	Retrospective	(21)
6	Wang, K., et al.	80	34	114	on admission	Retrospective	(22)
7	Huang, L., et al.	5	3	8	on admission	Case Series	(23)
8	Luo, Z., et al.	4	8	12	on admission	Retrospective	(24)
9	Fang, X., et al.	6	8	14	on admission	Case Series	(25)
10	Peng, S., et al.	2	9	11	on admission	Case Series	(26)
11	Guan, C.S., et al.	30	23	53	on admission	Retrospective	(27)
12	Xu, X., et al.	12	78	90	on admission	Retrospective	(28)
13	Shi, H., et al.	2	34	36	on admission	Retrospective	(29)
14	Ding, X., et al.	12	35	47	on days 0. and 3.	Retrospective	(30)
15	Lomoro, P., et al.	25	17	42	on days 0. and 3.	Retrospective	(12)

16	Li, X., et al.,	91	40	131	on days 0. and 3.	Retrospective	(31)
17	Wang, X., et al.	54	958	1012	on days 0. and 4.	Retrospective	(32)
18	Zhou, Z., et al.	12	22	34	on days 0. and 4.	Retrospective	(33)
19	Nie, W., et al.	125	38	163	on days 0. and 4.	Retrospective	(34)
20	Liu, Z., et al.	50	22	72	on days 0. and 4.	Retrospective	(35)

The 13 of studies have CT findings on admission, seven of them on days 0. and 4. days. There were 2326 (N) Covid-19 patients with positive rRT-PCR test and chest CT finding GGO and Consolidation of patients during the first 0-4 days of fever onset or within the 0-4 days of admission to the hospital. 100 % of all cases included in our study have positive rRT-PCR test results. The research question is: "Should there be a finding of Consolidation accompanying to the diagnosis of chest CT within the first 4 days of fever or hospitalization? Is the rate of opacity and the consolidation same in the early stage Covid-19 positive patients?

3.2 Imaging Outcomes

Outcomes for Ground Glass Opacities: The Prevalence of GGO occurrence in studies included in the analysis is 82% (95% CI 61-92%). There is two study which are outlier, one is study "3" (20) and the other is study "19" (34), shown in Figure 3B. When outliers are corrected, the prevalence turns into 81% (95% CI 65-91%). The Line Charts of Outlier Studies for Ground Glass Opacity shown in Figure 3A and The Scatter Plot of Outlier Studies for Ground Glass Opacity shown in Figure 3B.

According to the prevalence results, the variability between studies is statistically significant (Estimate=1.49, se=0.15, Z=10.20, p< 0.001 CI 95% 1.21-1.78), and it is supported by Cochran's Q test's results that the heterogeneity detected is statistically significant (Q=85.44, df=19, p<0.001). The other test results that measure heterogeneity also support the Q test. Tau2= 0.26 (SE=0.1849) (CI 95% 0.12- 1.02), I2= 77.76% (CI 95% 63.09-93.31%) and H2= 4.50 (CI 95% 2.71-14.94). After the study is found to be heterogeneous, the random effect model is used in the meta-analysis where Prevalence is calculated, and The Prevalence of Ground Glass Opacity are shown with Figure 3C.

The funnel plot is the distribution graphic of the studies included in the meta-analysis according to the standard deviation and prevalence values and evaluate the presence of bias. To evaluate the bias of the Funnel Chart, Egger Regression Model was chosen in accordance with our data because the model evaluates on weights. Test for Funnel plot's asymmetry with value p<0.05 showed presence of bias (t=2.25, df=18, p=0.022), The Funnel Plot for Ground Glass Opacity shown in Figure 3D. To solve the bias in the study, we looked at the Funnel by removing the extreme values, but the result did not change (Egger test: t=2.29, df=15, p=0.018).

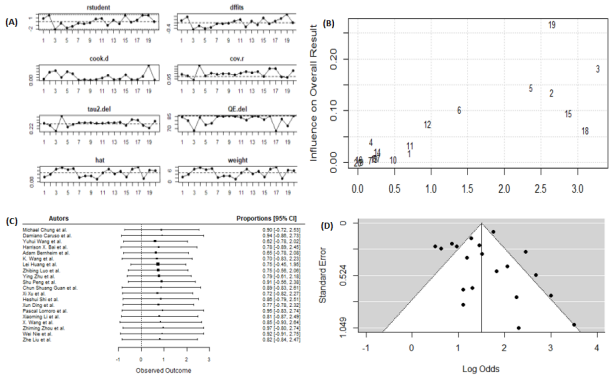

Figure 3. *GGO Results*

Sub-groups of the study were examined to investigate bias. Two groups were created according to CT imaging days, one was “on admission” and the other was “on 0 - 4 days”. For “on admission” Cochran Q test results showed heterogeneity (Q=33.70, df=12, p<0.050) and Prevalence=77% (95% CI PLO=71-82%). The Egger Regression Test for asymmetry of Funnel plot had the same bias (t=2.34, df=11, p=0.018). For CT images taken “on days 0 and 4” the Cochran Q test results had the same heterogeneity (Q=16.88, df=6, p<0.050) and there were no bias at this time for finding of CT images taken on days zero and fourth (Egger test: t=1.82, df=6, p=0.060). The prevalence for “on days 0 and 4” is 87% (95% CI PLO=82-90%).

Outcomes for Consolidation

The percentage of consolidation is 40 % (95% CI 25-56%). Study 17. (32) and 13. (29) outlier values, after correcting outliers the percentage turns into 47% (95% CI 37% - 57%). The Line Charts of Outlier Studies for Consolidation shown in Figure 4A and The Scatter Plot of Outlier Studies for Consolidation shown in Figure 4B.

According to the prevalence of consolidation, with Cochran’s Q test’s results shows that the heterogeneity detected is statistically significant (Q=602.53, df=19, p<0.001). The other test results that measure heterogeneity also support the Q test. Tau2 = 2.04 (CI 95% 0.70- 2.94), I2 = 96 % (CI 95% 91-97%) and H2 = 31.71 (CI 95% 11.58-45.53). After the study is found to be heterogeneous, the random effect model is used in the meta-analysis where prevalence is calculated, and the results are the prevalence of consolidation shown in Figure 4C .

The images belong to the funnel plot shows the studies spread all over the chart. The funnel plot for consolidation shown in Figure 4D. To examine the bias of the Funnel Chart, the Egger Regression Model (model=”lm”) result shows no presence of bias (t=-1.10, df=18, p=0.270). Sub-groups of the study were examined for consolidation prevalence, CT images of “on admission” have Prevalence=38% (95% CI PLO=26% -51%) and CT images taken “on days 0 and 4” have Prevalence= 48% (95% CI PLO=15% -83%).

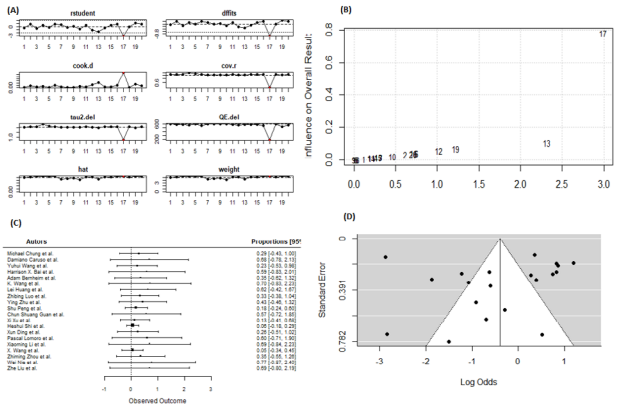

Figure 4. *Consolidation Results*

4. Discussion

The contribution of lung findings to Covid-19 disease diagnosis cannot be ignored, therefore many studies have been conducted on the sensitivity and specificity, by using RT-PCR as a reference and using chest CT images of Covid-19 as positive predictive value or as negative predictive value, just like Caruso, D., et al. found sensitivity 97% and specificity 56% or Dashraath, P., found 97% for sensitivity and 25% for specificity. Himoto, Y., et al.conducted a study with a series of 51 patients by founding chest CT and RT-PCR assay performed in 3 days, the sensitivity was 98% for CT and 71% for RT-PCR (p<0.001). (15-17)

In a study conducted in China, of 1014 patients, 59% had positive RT-PCR results, and 88% had positive chest CT scans. The sensitivity of chest CT in suggesting Covid-19 was 97% (95% CI, 95-98%). With negative RT-PCR result 75% (308/413) had positive chest CT finding; of 308, 48% were considered as highly likely cases, with 33% as probable cases that ultimately all cases received a positive test result. Another output of the same study: In the first CT measurements, the initial negative RT-PCR returned to positive with an average of 5.1 ± 1.5 days and initial positive and then negative RT-PCR the conversion took an average of 6.9 ± 2.3 days. (9)

At Hunan, China a study conducted for differentiating 219 Covid-19 patients from 205 patients with pneumonia without Covid-19, diagnostic capabilities of radiologists and three Chinese radiologists had sensitivity of 72%, 72%, 94% and specificity of 94%, 88%, 24%; four United States radiologists had a sensitivity of 93%, 83%, 73% and 73% and specificity of 100%, 93%, 93% and 100%. The most discriminating features for Covid-19 pneumonia were peripheral distribution (with 80% and 57%, p<0.001), GGO (91% and 68%, p<0.001) and vascular thickening (58% and 22%, p<0.001). (18)

It is understood that GGO is a very important parameter for diagnosis of Covid-19 disease in CT images. As a radiological finding in the lung, GGO turns to into Consolidation, which is a histopathological structure within an average of 0-4 days.

The percentage of GGO occurrence in studies included in our meta-analysis is 82 % (%95 CI 61-92 %). At the same time the percentage of consolidation is 40% (95% CI 37-92). Respectively in studies 3., 5., 6., 12., 17. with number of samples (n) 79, 256, 114, 90, 1012 the represent of GGO was 62%, 78%, 70%, 72%, 85% and consolidation was 29%, 58%, 70%, 13%, 5%. (20,21,22,28,32)

By showing observed value and variants of the studies: There were extreme values at study 12. with value yi=1.69, vi=0.076; study 13. (29) with value yi=2.74, vi=0.476, study 17. (yi=2.77, vi=0.017). (28,29,32)

According to the GGO prevalence results, the variability between studies is statistically significant (Estimate=1.49, se=0.15, Z=10.20, p< 0.001 CI 95% 1.21—1.78), and it is supported by Cochran's Q test's results that the heterogeneity detected is statistically significant (Q=85.44, df=19, p<0.001, I2=77.76%). Cochran's Q test's results for the prevalence of consolidation shows heterogeneity (Q=602.53, df=19, p<0.001, I2=96%).

In the positive CT findings, we know that GGO is present up to 5 days, on the fifth and the later days GGO changes into consolidation. This meta-analysis also shows same result; the Prevalence of GGO for early stage of Covid-19 is 82% and Consolidation's Prevalence is 40%.

5. Conclusion

This meta-analysis has provided an overview of early Chest CT findings of Covid-19 patients. In the analysis which the random effect model was applied, an inference about the population Prevalence value of GGO and Consolidation has been gained. The long incubation period explains the heterogeneity of analysis.

In the early stage of SARS-Cov-2 when fever and cough are observed, radiological findings have become vital in the rapid and early diagnosis. Chest CT can be a great benefit to the patients and to the public health surveillance at SARS-Cov-2 infection.

ABBREVIATIONS

GGO	:	Ground-Glass Opacity
CT	:	*Computed Tomography*
rRT-PCR	:	Real-Time Reverse Transcription–Polymerase Chain Reaction
SARS-Cov-2	:	Severe Acute Respiratory Syndrome Coronavirus 2
RNSA	:	The Research Network for a Secure Australia
RT-PCR	:	Reverse Transcription Polymerase Chain Reaction
RNAs	:	Viral Ribonucleic Acids
PRISMA	:	Preferred Reporting Items for Systematic Reviews and Meta-Analysis

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