

## ORIGINAL ARTICLE

# Incidence of white matter lesions in hospitalized COVID-19 patients: A meta-analysis

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## Abstract

**Objective:** Novel coronavirus disease 2019 (COVID-19) has been found to be associated with encephalopathy and brain imaging abnormalities. The identification of incident white matter lesions, known to be associated with cerebral microcirculatory failure and cerebrovascular disease, in COVID-19 patients is of clinical and scientific interest. We performed a meta-analysis to investigate the incidence of white matter lesions (WMLs) in hospitalized COVID-19 patients.

**Methods:** PubMed, EMBASE, and the Cochrane Library were searched for studies on brain imaging abnormalities in hospitalized COVID-19 patients. The terms used included “white matter lesions,” “white matter hyperintensity,” “COVID-19,” “coronavirus,” and “SARS-CoV-2.” A random-effects meta-analysis was conducted to obtain a pooled estimate of WML prevalence in hospitalized COVID-19 patients.

**Results:** A total of 4 eligible studies involving 362 patients (144 with WMLs and 218 without) were included in the meta-analysis. We found the pooled estimate of WML prevalence to be 20% (ES 0.20; 95% CI 0.00–0.54;  $p = .03$ ).

**Conclusions:** The estimated pooled prevalence rate of WMLs was approximately 20% in hospitalized COVID-19 patients, albeit lower than the crude prevalence rate (39.8%).

## KEYWORDS

cerebrovascular disease, COVID-19, leukoaraiosis, microcirculation, SARS-CoV-2, stroke, white matter lesions

## 1 | INTRODUCTION

There is mounting evidence that coronavirus disease 2019 (COVID-19) is associated with central nervous system involvement,<sup>1,2</sup> with several reports of patients exhibiting neurological manifestations and brain imaging abnormalities.<sup>3</sup> Among the notable neuroimaging, findings in this population are white matter lesions (WMLs). WMLs, also referred to as leukoaraiosis or white matter hyperintensity (WMH), are areas of hyperintensity in cerebral white matter as seen on magnetic resonance imaging (MRI).<sup>4-6</sup> Cerebrovascular dysfunction and cerebral microcirculatory failure have been implicated in hypoperfusion and white matter damage.<sup>7</sup> While WMLs have been reported in the setting of COVID-19,<sup>3,8</sup> there are limited data surrounding their incidence in patients with COVID-19. This meta-analysis sought to obtain a pooled estimate of the prevalence of WMLs in hospitalized COVID-19 patients. Our primary hypothesis is that there is a high prevalence of WMLs in hospitalized patients with COVID-19.

## 2 | MATERIALS AND METHODS

### 2.1 | Literature search: Identification and selection of studies

The databases of EMBASE, PubMed, and Cochrane Central Register of Clinical Trials databases were used as the search engines. Articles published between January 2020 and June 2021 were included in the search. The search terms included: "white matter lesions" or "leukoaraiosis" or "white matter hyperintensity" and "COVID-19" or "coronavirus" or "SARS-CoV-2." Additionally, studies were limited to those that were in the English language and conducted on humans. The search was conducted on the July 10, 2021. The complete search strategy is available in the Appendix S1 (Search Strategy). The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart shows the studies included in the meta-analysis (Figure 1). This study adheres to the guidelines outlined in the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Table S1) and PRISMA 2020 (Table S2) checklists.

### 2.2 | Inclusion and exclusion criteria

Studies were eligible for inclusion if they met the following criteria: (1) age  $\geq 18$  years; (2) patients with a confirmed diagnosis of COVID-19 in the hospital; (3) patients who received brain imaging; (4) availability of data on non-specific WMLs in patients; and (5) studies with a sample size of  $>20$  patients. The exclusion criteria were (1) studies not in English; (2) animal studies; (3) duplicated publications; (4) full-text articles not available; (5) systematic reviews, meta-analyses, or letters; and (6) studies presented in the abstract form, with relevant data on white matter lesions not available.

### 2.3 | Data extraction

Titles and abstracts were first screened on Endnote to identify and exclude articles that were outside the field of interest, were systematic reviews or meta-analyses, or mismatched the eligibility criteria for other reasons. The remaining articles then underwent a comprehensive assessment to determine whether they should be included in the systematic review or meta-analysis. The reference list of obtained articles was also examined. The screening was conducted independently by two experienced investigators. In case of disagreement between authors, a consensus was reached through discussion. A data extraction sheet was used to extract the following data from each study: 1) baseline demographics: author, country, and year of publication; 2) study population: age of patients, sample size, baseline clinical characteristics, need for ventilation, and proportion of patients in the intensive care unit (ICU); and (3) outcome measures: prevalence of leukoaraiosis in patients. All studies were conducted on hospitalized COVID-19 patients. However, three studies only included patients who developed neurological symptoms, with one of these being further restricted to patients within the ICU. The remaining studies examined all COVID-19 patients hospitalized within a given time frame. Where applicable, mean and standard deviation were estimated from the sample size, median, and range using the method published by Wan et al.<sup>9</sup>

### 2.4 | Quality assessment of included studies

The methodological quality of each study was assessed independently by two researchers using modified Jadad analysis.<sup>10</sup> The modified Jadad scale evaluates study quality based on randomization, blinding, description of withdrawals/dropouts, inclusion/exclusion criteria, assessment of adverse events, and methods used for statistical analysis. Using this scale, studies may be scored from 0 to 8. Studies included in the meta-analysis all obtained a score of 3. Each study was also separately assessed for risk of funding bias using a 4-point scale that scored studies from 0 (low potential for bias) to 3 (high potential for bias).<sup>11</sup> The absence of industry funding was not taken to signify an absence of bias, but the presence of industry funding or conflicts of interest was assumed to be an indicator of bias. None of the included studies were found to have high potential for bias.

### 2.5 | Statistical analysis

All statistical analyses were performed using STATA (Version 13.0, StataCorp LLC). This study investigated the proportion of white matter lesions in patients with COVID-19. The "metaprop" STATA command was used to pool proportions by performing a random-effects meta-analysis of proportions obtained from the individual studies.<sup>12</sup> Random-effects modeling was performed using the DerSimonian and Laird method. Forest plots were generated to study overall effects. To stabilize the variances, Freeman-Tukey double arcsine

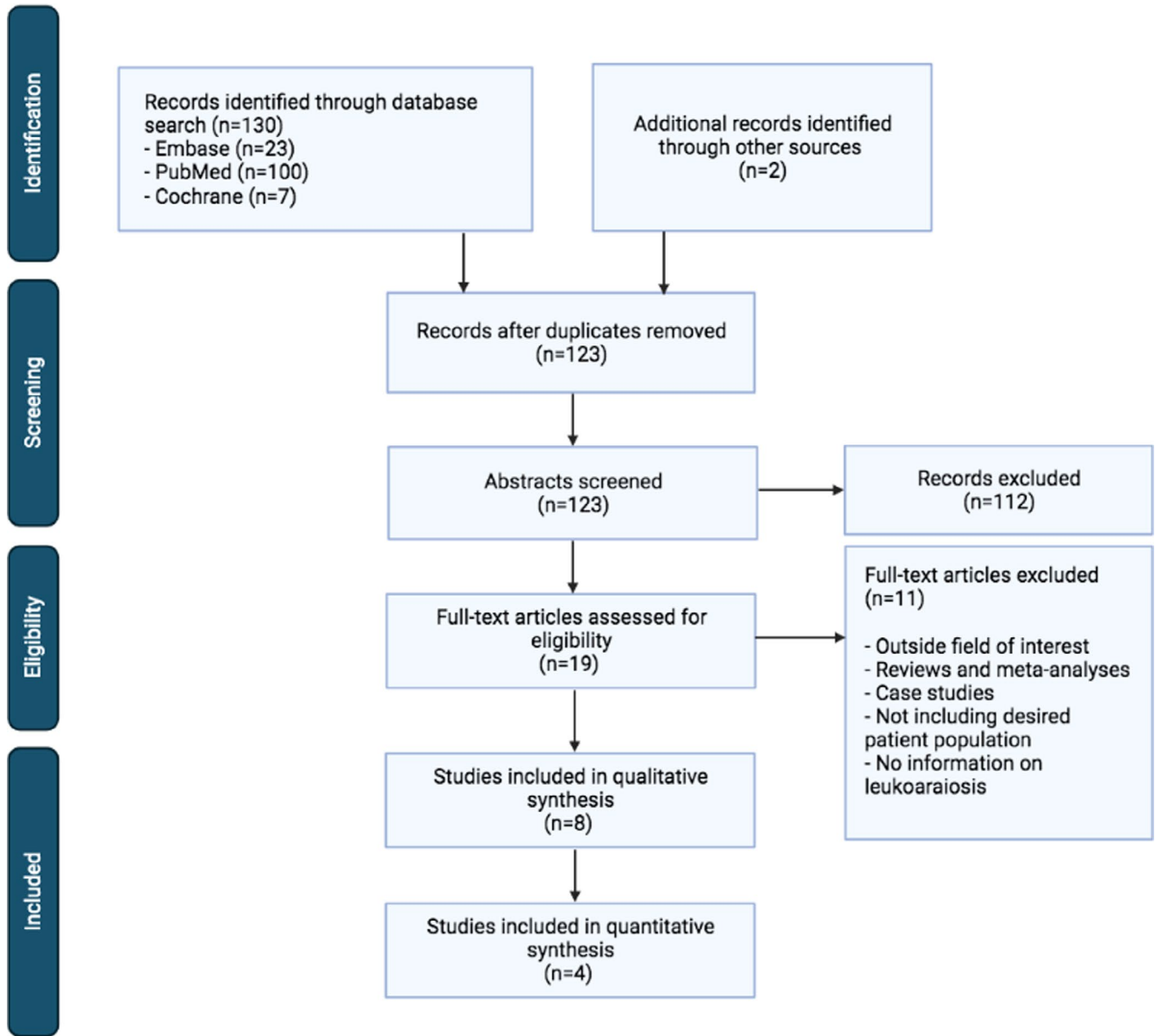


FIGURE 1 PRISMA flowchart showing the steps followed during the study selection process

transformation was applied to calculate the pooled estimates. The heterogeneity was estimated from the inverse-variance fixed-effect model and quantified using the  $I^2$  measure ( $I^2 < 40\% = \text{low}$ ,  $30\% - 60\% = \text{moderate}$ ,  $50\% - 90\% = \text{substantial}$ , and  $75\% - 100\% = \text{considerable}$ ). An estimate of between-study variance (tau-squared or  $\tau^2$ ) was also reported. The significance tests, in terms of Z-statistics and p-values, were reported. A p-value  $< .05$  was considered significant.

### 3 | RESULTS

#### 3.1 | Description of included studies

This meta-analysis included 4 case series reporting on brain imaging findings in COVID-19 patients, with a cumulative cohort of 362 patients.<sup>13-16</sup> Of these, 144 (39.8%) had WMLs on brain imaging, and

219 were male (reported for 342 patients). The mean age  $\pm$ SD (reported for 342 patients) was  $63.2 \pm 15.1$ . The clinical characteristics of all included studies are shown in Table 1. The Jadad analysis and funding bias analysis for each study can be found in Table S3.

#### 3.2 | Incidence of white matter lesions in COVID-19 patients

All four included studies reported on the incidence of WMLs in COVID-19 patients. A pooled estimate of 20% was found (ES 0.20; 95% CI 0.00–0.54;  $z = 2.15$ ;  $p = .03$ ) (Figure 2 and Table S4). Notably, there was considerable heterogeneity between the included studies ( $I^2 = 96.86\%$ ,  $p < .001$ ). The estimate of between-study variance ( $\tau^2$ ) was 0.50. The estimated pooled prevalence was lower than the crude prevalence rates (39.8%) observed in this study.

TABLE 1 Clinical characteristics of studies included in the meta-analysis

Author	Year	Study design	Country	Cohort	Population
Chougar et al.	2020	Retrospective	France	73	COVID-19 patients presenting with acute neurological symptoms
Radmanesh et al.	2020	Retrospective	USA	242	All COVID-19 patients hospitalized within given time frame
Kandemirli et al.	2020	Retrospective	Turkey	27	COVID-19 patients in the ICU, who developed acute neurological symptoms
Mahammedi et al.	2020	Retrospective	Italy	20	COVID-19 patients who developed acute neurological symptoms

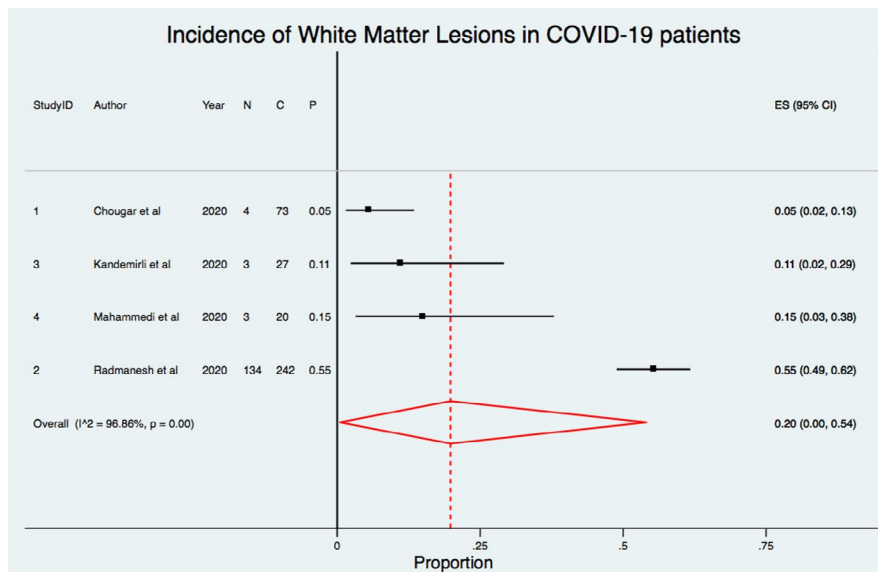


FIGURE 2 Forest plot showing the estimated prevalence of white matter lesions in hospitalized COVID-19 patients. Abbreviations: N, number of patients with white matter lesions; C, number of hospitalized COVID-19 patients; P, proportion of COVID-19 patients with white matter lesions

## 4 | DISCUSSION

Our meta-analysis provides a pooled estimate of the incidence of WMLs in hospitalized COVID-19 patients. To our knowledge, this is the first meta-analysis to investigate WML prevalence in this population. Our findings indicate that the estimated pooled prevalence of WMLs in hospitalized COVID-19 patients is approximately 20%. This is a conservative estimate in comparison with previous epidemiological studies investigating WML prevalence in both hospitalized patients and the general population. Thus, this suggests that the prevalence of WMLs in hospitalized COVID-19 patients may be lower than in non-COVID settings. We postulate that the current meta-analysis, which included cross-sectional studies and excluded case reports from a well-characterized clinical cohort of hospitalized patients, reflects the case-mix seen in real-world clinical settings.

Due to the limited epidemiological data surrounding leukoaraosis, its prevalence in the general population is poorly elucidated. Two recent studies conducted in hospitalized cohorts in China found WMLs to be present in 58.3% and 81.4% of patients, respectively.<sup>17,18</sup> Moreover, community-based samples in healthy

populations from Australia and the Netherlands have also shown high incidences, at 50.9% and 95%, respectively.<sup>19,20</sup> Importantly, subjects in the cohort from the Netherlands were significantly older than those included in other studies. Conversely, WML prevalence in a young (16–65) and healthy cohort from the United States of America was shown to be as low as 5.3%.<sup>21</sup> Similarly, a study in a cohort aged 1–45 in China also reported a relatively low prevalence of 25.94%.<sup>22</sup> When considering these historically reported rates, the 20% prevalence found in our study is lower than expected for our cohort of COVID-19 patients with a mean age of 63.2 years. The reasons for this finding are unclear. However, our results must be interpreted within the context of our study's limitations.

Our study has several limitations. First, due to the limited literature on brain imaging findings in COVID-19 patients, our meta-analysis included only 4 studies and thus may have been underpowered to detect significant effects. Notably, a separate analysis of studies with sample sizes of 15 and above was also conducted,<sup>13–16,23,24</sup> and yielded a pooled estimate of WML prevalence of 42% (ES 0.42; 95% CI 0.17–0.68;  $p < .001$ ) (Figure S1). Thus, it is possible that examination of results from a greater

Baseline characteristics					
Age (mean ±SD)	Male (n, %)	Imaging modality	WML (n, %)	ICU (n, %)	Ventilation (n, %)
58.5 ± 15.6	48 (65.8)	FLAIR MRI	4 (5.5)	38 (52)	NA
68.7 ± 16.5	150 (62)	CT (207 patients), T2 MRI (11 patients), both (24)	134 (55.4)	NA	NA
62.4 ± 13.3	21 (78)	FLAIR MRI	3 (11.1)	27 (100)	27 (100)
NA	NA	T2/FLAIR MRI	3 (15)	NA	NA

number of studies may reveal a higher prevalence. Second, all included studies were limited by their retrospective study design and small sample sizes. We recommend future large-scale prospective studies to further investigate WML prevalence in hospitalized COVID-19 patients. Third, there was heterogeneity within the pooled cohort, as three studies only included patients who developed neurological symptoms, while one study included all COVID-19 patients hospitalized within a specific timeframe. Moreover, one study was also restricted to patients in the intensive care unit (ICU), while the others were not. Additionally, there was variation across studies in the imaging modality used to visualize the brain. However, given that we used the random-effects model for our statistical analysis, we postulate that the heterogeneity arising from these factors was minimized by our methodology. Finally, the included studies reported purely on the presence of any WMLs, without any assessment of lesion severity. Thus, we did not examine the incidence of moderate to severe WMLs in patients with COVID-19. This reduces the clinical relevance of our findings, as previous studies found WML severity to be more clinically relevant than presence.<sup>25</sup> Future studies investigating the association of WML severity with in-hospital and long-term outcomes in COVID-19-infected patients are warranted. Importantly, it must also be noted that our meta-analysis simply provides an estimate of WML prevalence in COVID-19 patients. We do not have sufficient data to suggest that COVID-19 is associated with an increased risk of WMLs or vice versa. There is a need for longitudinal studies examining the progression of WMLs in COVID-19 patients through serial brain imaging. We also acknowledge that, albeit, reported percentage of non-specific supratentorial WMLs in hospitalized COVID-19 patients in our study is uncharacteristically low; the majority of included patients are those within the United States, a population in which proportion of such lesions is quite low,<sup>21</sup> much lower than that reported in the current study.

In conclusion, this meta-analysis demonstrated a pooled prevalence estimate of 20% of WMLs among hospitalized COVID-19 patients. Thus, our findings indicate that hospitalized COVID-19 patients do not exhibit a higher prevalence of WMLs than the general population. Further studies on the association of COVID-19

with WMLs are required to clearly delineate the putative role of COVID-19 in WML pathogenesis.

## 5 | PERSPECTIVES

COVID-19 has been linked to encephalopathy and abnormalities on brain imaging.

The observation of incident WMLs in COVID-19 patients is of clinical, public health and scientific relevance.

To fully elucidate the possible involvement of COVID-19 in WML pathogenesis, more research on the relationship of COVID-19 with WMLs is needed.

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### CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

### AUTHOR CONTRIBUTION

SMMB conceived the study, contributed to the planning, drafting, and revision of the manuscript; and supervision of the student. SMMB encouraged AR to investigate and supervised the findings of this work. AR and SMMB wrote the first draft of this paper. All authors contributed to the revision of the manuscript, and approved the final draft of the manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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