Sistematic review article

Histopathological findings in lungs of COVID-19 infected subjects. A systematic review and meta-analysis

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Abstract
Introduction. COVID-19 is a new disease that required prompt results from research. One approach to understanding its pathophysiology is to know the histopathological damage generated in the lungs of those affected. **Objective.** To provide a rigorous summary of the available evidence on pulmonary histopathological findings in patients with COVID-19. **Methodology.** A systematic review with a meta-analysis of proportions was developed. Primary studies of any design that had primary data on histopathologic findings of lungs in COVID-19 patients were included. Reviews and guidelines were excluded. Data sources were the Living OVerview of Evidence centralized repository, PubMed/Medline, LitCovid, the World Health Organization COVID-19 database, and medRxiv until April 3, 2021. A risk of bias assessment was performed using the Joanna Briggs Institute tools for case series and case reports. Each histopathologic pulmonary finding was extracted. The frequencies found were calculated, and the data for the most frequent findings were summarized in meta-analyses using the Der Simmonian-Liard random-effects method. Heterogeneity was measured. **Results.** Inclusion criteria were met by 69 articles totaling 594 subjects. Thirty-five articles were at low risk of bias. Meta-analysis of proportions showed diffuse alveolar damage in 0.62 (95 % CI 0.51-0.72), I^2 59 % ($p < 0.01$), in its early phase (85.14 %). **Conclusion.** Early diffuse alveolar damage was the most frequent histopathological finding in lung specimens from patients with COVID-19.

Keywords
COVID-19, systematic review, autopsies, pathology, lung.

Resumen
Introducción. La COVID-19 es una nueva enfermedad que requería resultados prontos provenientes de la investigación. Un abordaje para la comprensión de su fisiopatología es conocer el daño a nivel histopatológico que genera en los pulmones de los afectados. **Objetivo.** Proveer un resumen riguroso de la evidencia disponible sobre los hallazgos histopatológicos pulmonares en pacientes con COVID-19. **Metodología.** Se desarrolló una revisión sistemática con metaanálisis de proporciones. Se incluyeron estudios primarios de cualquier diseño que tuvieran datos primarios de hallazgos histopatológicos de pulmones en pacientes COVID-19. Se excluyeron revisiones y guías. Las fuentes de información fueron el repositorio centralizado Living OVerview of Evidence, PubMed/Medline, LitCovid, la base de datos COVID-19 de la Organización Mundial de la Salud, y medRxiv hasta el 3 de abril 2021. La evaluación del riesgo de sesgos se realizó utilizando las herramientas del Instituto Joanna Briggs para series de casos y reportes de casos. Se extrajo cada dato de hallazgo pulmonar histopatológico. Se calcularon las frecuencias encontradas y los datos de los hallazgos más frecuentes fueron resumidas en metaanálisis usando el método de efectos aleatorios de Der Simmonian-Liard. Se midió la heterogeneidad. **Resultados.** Los criterios de inclusión fueron cumplidos por 69 artículos sumando 594 sujetos. Presentaron bajo riesgo de sesgos 35 artículos. El metaanálisis de proporciones mostro daño alveolar difuso en 0,62 (IC 95 % 0,51-0,72), I^2 59 % ($p < 0,01$), en su fase temprana (85,14 %). **Conclusión.** El daño alveolar difuso temprano fue el hallazgo histopatológico más frecuente en muestras pulmonares de pacientes con COVID-19.

Palabras clave
COVID-19, revisión sistemática, autopsia, patología, pulmón.

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Hallazgos histopatológicos pulmonares asociados a COVID-19. Una revisión sistemática y metaanálisis

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Conflicts of interest:
The authors declare there are no conflicts of interest.

Introduction

COVID-19 is an infection caused by the SARS-CoV-2 coronavirus. It was initially identified in Wuhan, China, on December 31, 2019; three months later, nearly half a million infections had been identified across 197 countries, leading the World Health Organization to declare a COVID-19 pandemic on March 11, 2020[1,2].

The main source of SARS-CoV-2 transmission is the airborne route, through droplets produced in the respiratory tract and by contact. An average incubation period of 5.1 days (95 % CI, 4.5 to 5.8 days) has been reported, but variations may occur depending on the patient's immune status[1]. The most frequently reported mild to moderate symptoms are fever 88.7 % (95 % CI 84.5-92.9 %), cough 57.6 % (95 % CI 40.8-74.4 %), and dyspnea 45.6 % (95 % CI 10.9-80.4 %)[3], with 17.5 % of infected patients being asymptomatic[1]. Complications occurred in 20.3 % (95 % CI 10-30.6 %) and the most frequent complications were: acute respiratory distress syndrome at 32.8 % (95 % CI 13.7-51.8 %); acute cardiac damage at 13 % (95 % CI 4.1-21.9 %), acute renal damage 7.9 % (95 % CI 1.8-14 %) and shock 6.2 % (95 % CI 3.1-9.3 %)[3]. In relation to mortality, a variation from 0.5 % to 13.9 % (95 % CI 6.2-21.5 %)[2,4] has been described, depending on the context and age groups in which they have been reported.

Laboratory findings described for the disease are hypoalbuminemia 75.8 %, (95 % CI 30.5-100 %), high C-reactive protein 58.3 % (95 % CI 21.8-94.7 %), high lactate dehydrogenase (LDH) 57 % (95 % CI 38-76 %), lymphopenia 43.1 %, (95 % CI 18.9-67.3 %), and high erythrocyte sedimentation rate 41.8 % (95 % CI 0.0-92.8 %)[5].

Initially, there were two theories about the pathophysiology of respiratory distress syndrome; the first dealt with direct damage to lung tissue that generates diffuse alveolar damage. It emphasizes the central role of diffuse injury to the epithelium up to the involvement of the endothelium of the distal pulmonary acini[3]; the second, which presumes that COVID-19 generates indirect damage resulting from a complication caused by coagulopathy and thrombosis. The endothelial injury caused by the disease breaks pulmonary vessel regulation, producing a ventilation-perfusion imbalance that promotes thrombogenesis and thrombosis[4]. Indirect clinical findings that supported this latter theory are as follows: a. High levels of D-dimer reported in several patients; b. Reports of clinical improvement of patients with heparins; c. High incidence of thrombosis in critically ill patients; d. and some references to findings reported in autopsies[4,5].

Histopathological examinations of the affected lungs could show the morphological changes and guide a better understanding of the pathophysiology of respiratory failure, respiratory distress syndrome, and consequent death. Several reports on these findings have been published until April 2021, so it might be appropriate to make a systematized summary through an innovative and agile process with technological tools, which is why the present study aims to provide a systematic review with meta-analysis of the evidence available at that date, on the pulmonary histopathological findings of autopsies and biopsies of patients with COVID-19.

Methodology

This systematic review has been prepared according to the PRISMA 2020 guidelines[6] and is part of a global project, with a general protocol established shared objectives and multiple evidence synthesis methodologies. This was conducted in parallel by working groups, which dealt with different questions related to COVID-19. This protocol was previously published[7]. The protocol for this specific systematic review was adapted to their requirements and registered in the PROSPERO platform obtaining the registration number CRD42020190598. A core team called the "COVID-19 L·OVE Working Group" coordinated the tasks supporting the self-research of all questions and provided methodological support. This question was submitted by the author team and accepted by this core team to participate in the Global Project[7].

Eligibility criteria

The inclusion criteria for studies were: any quantitative primary study design and systematic reviews with raw data allowing calculation of frequencies for each specific histopathological finding found in the lungs of patients with COVID-19, in which any approach [autopsies (open or minimally invasive), biopsies] was used, with full text available, in any publication status and any language approachable for translation.

The excluded studies were: animal findings, findings of coronaviruses other than SARS-CoV2, cases of prolonged or convalescent period COVID, editorials, commentaries, narrative reviews/autopsy biosafety guidelines, or any other documents on autopsy procedures or biosafety protocols for specimen handlers, articles classifying

causes of death or only with photographs of histopathological findings but without textual description, as well as articles describing molecular methods of analysis or studying inflammatory markers.

Types of participants

Histopathological findings had to come from samples of confirmed COVID-19 cases, defined and accepted by the study authors (Rt-PCR reverse polymerase chain reaction, chest X-ray, chest CT scan, or any other approved diagnostic method), regardless of age, sex, outcome (alive or deceased), and in-hospital or outpatient management.

Condition Type

COVID-19 active.

Type of results

Primary outcome: Individualized pulmonary histopathologic findings. This variable was left open to introducing all possible findings and not to exclude any of them.
Secondary outcomes: Demographic characteristics of the included subjects, place of death (intra-hospital/extra-hospital) (Table 1).

Sources of Information

Electronic sources

The principal source used was the Epistemonikos Database[8], and within this, the L·OVE platform[9]. The Epistemonikos platform maintenance team conducted the literature search using the following approach: 1. The search terms relevant to the population and results were identified as components of the search strategy, using Word-2vec technology for the body of documents available in the database; 2. There was a discussion on search terms with content and method experts to identify relevant, irrelevant, or missing terms; 3. A sensitive Boolean strategy was created to track relevant terms; 4. Items not detected by Boolean were iteratively analyzed; and 5. The strategy was refined.

The artificial intelligence algorithm used in the Coronavirus/COVID-19 topic of the L·OVE platform provided instant notifications by identifying articles with a high similarity of being eligible. The authors tracked those notifications related to pulmonary histologic findings on COVID-19 from May 1, 2020, to April 3, 2021. Additional searches were performed using highly sensitive descriptors in PubMed/MEDLINE and the WHO database on Covid-19. The following electronic databases were also searched for full text: LitCovid, BioRxiv, and medRxiv. These databases were also searched until April 3, 2021. There were no restrictions on study design, publication status, or language in any search.

Other sources

To identify articles that may have been left out of the initial electronic search, the following was as follow: 1. The reference list of other systematic references and primary studies was screened; 2. The reference list of narrative reviews and other papers was sifted; 3. A review of UN and regulatory agency websites or databases reporting on COVID-19 was conducted.; 4. E-mails were sent to contact each of the authors of the included studies to request additional publications and more data on the studies that were unclear or not mentioned.

Search strategy

The following search strategy was used in Epistemonikos database and PubMed/MEDLINE (coronavir* OR coronovirus* OR "corona virus" OR "corona virus" OR "corona virus" OR "corono virus" OR "corono virus" OR hcov*OR "COVID-19" OR covid19* OR "covid 19" OR "2019- nCoV" OR cv19* OR "cv- 19" OR "cv 19" OR "n-cov" OR ncov* OR "sars-cov-2" OR "sarscov2" OR (wuhan* AND (virus OR viruses OR viruses OR viral) OR coronav*) OR (covid* AND (virus OR viruses OR viral)) OR "sars-cov" OR "sars-cov" OR "sars-cov" OR "sars- coronavirus" OR "severe acute respiratorysyndrome" OR "mers-cov" OR "mers cov" OR "middle east respiratory syndrome "OR "middle east respiratory syndrome "OR "middle east respiratory syndrome" OR "COVID- 19- related" OR "SARS-CoV-2-related" OR "SARS-CoV2-related" OR "2019-nCoV-related" OR "cv-19-related" OR "n-cov-related") AND "autopsy" OR "autopsies" OR "pathology "OR "pathology features" OR "histology" OR "biopsy" OR "thrombosis".

Selection process

The literature search results in Epistemonikos were automatically into the L·OVE Platform (automated finding), where duplicity was identified through an algorithm. It compared unique identifiers (database ID, DOI, study ID record) and citation details (e.g., authors' names, journal, year of publication, volume, number of pages, article title, and article abstract).

On the L·OVE platform, two investigators independently screened the titles and abstracts submitted by the search against the inclusion criteria. Besides, they obtained full texts for all titles that appeared to meet the inclusion criteria or additional analysis to decide inclusion. The two investigators

Table 1. Characteristics of the studies and patients included

Author, peer-reviewed or preprint journal, DOI, and source of funding	Number of patients	Participants included	Place of death	Diagnostic method	City, country	Sample collection
Case series						
Lax SF, 2020 Journal DOI: 10.7326/m20-2566. No funding[77].	11	8 male in strata age: 1 aged 90 years; 5 aged 80years; 1 aged 70 years; 1 aged 60 years. 3 female: 2 aged 80 years and 1 aged 70 years	Intra-hospital	RT-PCR	Styria, Austria	Open autopsy
Bryce C, 2020 Preprint MedRxiV DOI: 10.1101/2020.05.18.20099960 No funding[49].	25	Gender distribution is no clear. Average age 67.5 years (95 % CI 34-84)	Intra-hospital	RT-PCR	New York, USA	Open autopsy
Wichman D, 2020 Journal DOI: 10.7326/M20-2003 Funded by U of Hamburgo[50]	12	9 M and 3 F. Average age 73 years	2 extra-hospital and 10 Intra-hospital	RT-PCR	Hamburg, Germany	Open autopsy
Remmelink M, 2020 Journal DOI: 10.1186/s13054-020-03218-5 Erasmos funding for biomedical research[51].	17	12 M; 5 F. Average age 82.5 years	Intra-hospital	RT-PCR	Brussels, Belgium	Open autopsy
Previtale G, 2020 Journal DOI: 10.1016/j.thromres.2020.06.042 No funding[52]	35	Adults over 18 years: 26 M; 9 F	Intra-hospital	RT-PCR	Bergamo, Italy	Open autopsy
Carsana L, 2020 Journal DOI: 10.1016/ S1473-3099(20)30434-5 No funding[5].	38	33M, 5F. Average age 69 years	Intra-hospital	Nasopharyngeal swab	Milan and Bergamo, Italy	Open autopsy
Fox SE, 2020 Journal DOI: 10.1016/S2213-2600(20)30243-5 No funding[53]	10	No data on gender, only African-American ethnicity. Average age 63 years.	Intra-hospital	RT-PCR	New Orleans, USA	Open autopsy
Prilutskiy A., 2020 Journal Boston University[54]	4	3 M, 1 F. Average age 75 years	Intra-hospital	RT-PCR	Boston, USA	Open autopsy
Ackermann M, 2020 Journal three fundings: INS, Botnar Research Center for Child Health and the European Research Council[74].	7	5 M, 2 F. Average age 68 years for males and 80 years for females	It is not clear	Nasopharyngeal swab	Hanover, Germany	Open autopsy
Duarte-Neto AN, 2020 Journal Fundacao de Amparo a Pesquisa do Estado[78].	10	5 M, 5 F. Average age 69 years	Intra-hospital	RT-PCR in 9 and 1 clinical	Sao Paulo, Brasil	Open autopsy
Menter T, 2020 Journal No mention of the funding source[57]	21	17 M, 4 F. Average age 76 years	Intra-hospital	RT-PCR	Basel, Switzerland	Open autopsy
Schaefer IM, 2020 Journal There are several sources of funding. Main: INS, PhAST diagnostic, Astra Zeneca and Roche/Genentech[61]	7	5 M, 2 F Average age 66 years	Intra-hospital	RT-PCR	Boston, USA	Open autopsy
Konopka K, 2020 Journal No funding declared[3]	8	5M, 3 F Average age 55 years	4 intra-hospital, 4 extra-hospital	RT-PCR	Michigan, USA	Open autopsy
Deinhardt-Emmer S, 2020, Preprint Carl Zeiss Foundation [59]	11	7 M, 4 F Average age 72.3 years	Intra-hospital	RT-PCR	Greiz and Jena, Germany	Open autopsy
Youd E, 2020 Journal No funding[60]	9	4 M, 5 F Average age: 75 years M 69 years F	Extra-hospital	RT-PCR	Cambridge, United Kingdom	Open autopsy
Schaller T, 2020 Journal No funding[58]	10	7 M, 3 F Average age 79 years	Intra-hospital	RT-PCR	Augsburg, Germany	Open autopsy

Author, peer-reviewed or preprint journal, DOI, and source of funding	Number of patients	Participants included	Place of death	Diagnostic method	City, country	Sample collection
Rapkiewicz AV, 2020 Journal Intramural research Program INS[62]	7	3 M, 4 F Average age 57.4 years	Intra-hospital	RT-PCR	New York, USA	Open autopsy
Wu JH, 2020. Journal Funding is not clear[63]	10	7M, 3 F Average age 70 years	It is not clear	RT-PCR	Wuhan, China	Percutaneous ultrasonography-guided cutting biopsy
Bradley BT, 2020 Journal No funding[64]	14	6M, 8 F Average age 73.5 years	It is not clear	RT-PCR	Washington, USA	Open autopsy
Copin M-C, 2020 Journal No mention of the funding source[65]	6	No characteristics reported	It is not reported	Hisopado nasofaringeo	Lille, France	Open autopsy
Skok S, 2020 Journal Open Access Funding Only[66]	28	17 M, 11 F Average age 72 years	Intra-hospital	RT-PCR	Styria, Austria	Open autopsy
De Michele S, 2020 Journal No mention of the funding source[67]	40	28 M, 12 F Average age 71.5 years	Intra-hospital	RT-PCR	New York, USA	Open autopsy
Kommoss FKF, 2020 Journal 10.3238/arztebl.2020.0500 No funding[68]	13	10 M, 3 F Average age 74.61 years	Intra-hospital	RT-PCR	Heidelberg, Germany	Open autopsy
Valdivia-Mazeyra M, 2020 Journal No funding[69]	18	10 M, 8 F Average age 61 years	Intra-hospital	RT-PCR	Madrid, Spain	11 open autopsies, 7 minimally invasive biopsies
Hanley B, 2020 Journal Funding Imperial Biomedical Research and Wellcome Trust[70]	10	7 M, 3 F Average age 75 years	Intra-hospital	RT-PCR	London and Oxon, United Kingdom	9 autopsies, 1 percutaneous biopsy
Grosse C, 2020 Journal 10.1016/j.carpath.2020.107263 No funding[71]	14	9 M, 5 F Average age 80.6 years	Intra-hospital	RT-PCR	Lintz, Austria	Open autopsy
Borczuk AC, 2020 Journal 10.1038/s41379-020-00661-1 No mention of the funding source[72]	68	47 M, 21 F Average age 73 years	It is not clear	RT-PCR	New York, USA and Padua, Italy	Open autopsy
Roden AC, 2020 Journal 10.5858/arpa.2020-0491-SA No mention of the funding source[73]	8	7 M, 1 F Average age 79 years	Intra-hospital	RT-PCR	Minnesotta, USA	Open autopsy
Nadkarni GN, 2020 Journal 10.1016/j.jacc.2020.08.041 Funded by INS[55]	26	16 M, 10 F Average age 64.61	Intra-hospital	Nasopharyngeal swab	New York, USA	Open autopsy
Jiang T Journal 10.1186/s12959-020-00256-5 The National Key R&D Program of China and the National Natural Science Foundation of China[75]	9	5M, 4 F Average age 69 years	Intra-hospital	RT-PCR	Wuhan, China	Open autopsy
Falasca L, 2021 Journal 10.1093/infdis/jiaa578 There have been several foundation and government financings[76]	22	15 M, 7 F Average age by comorbidity: 76 years with comorbidity and 48,5 without comorbidity	Intra-hospital	RT-PCR	Rome, Italy	Open autopsy
Case reports						
Yan L, 2020 Journal 10.588/arpa.2020-0217-SA No funding[13]	1	44-year-old Hispanic woman	Extra-hospital	RT-PCR	Texas, USA	Open autopsy

Author, peer-reviewed or preprint journal, DOI, and source of funding	Number of patients	Participants included	Place of death	Diagnostic method	City, country	Sample collection
Sekulic M, 2020 Journal 10.1093/AJCP/AQAA091 No funding[14]	2	2 M: 54 and 81 years	Intra-hospital	RT-PCR	Ohio, USA	Open autopsy
Lacy JM, 2020 Journal 10.1097/PAF.0000000000000567 No mention of the funding source[15]	1	58-year-old female	Extra-hospital	RT-PCR	Wisconsin, USA	Open autopsy
Tian S, 2020 Journal 10.1016/j.jtho.2020.02.010 No mention of the funding source[17]	2	1 M aged 73 years 1 F aged 84 years with lung cancer	1 Intra-hospital Other not deceased	RT-PCR	Wuhan, China	Surgical biopsy
Suess C, 2020 Journal 10.1007/s00414-020-02319-8 Funded by Institute of Legal Medicine Switzerland [16]	1	59-year-old man	Extra-hospital	Hisopado nasofaringeo	St Gallen, Switzerland	Autopsy
Tian S, 2020 Journal 10.1038/s41379-020-0536-x No mention of the funding source[34]	4	3 M, 1 F Average age 73 years	Intra-hospital	RT-PCR	Wuhan, China	Core biopsy
Yao XH, 2020 Journal 10.3760/cma.j.cn112151-20200312-00193[18]	3	2M aged 63 and 69 years 1 F aged 79 years	Intra-hospital	RT-PCR	Chongqing, China	Minimally invasive autopsy
Adachi T, 2020 Journal 10.3201/eid2609.201353 Funding by Japan Agency for Medical Research[19]	1	1 84-year-old man	Intra-hospital	RT-PCR	Tokio, Japan	Open autopsy
Buja LM, 2020 Journal 10.10106/j.carpath.2020.107233 Local funding[20]	3	1 Hispanic male aged 62 years 1 afroamerican male aged 34 years 1 Hispanic male aged 48 years	1 intra-hospital 2 extra-hospital	RT-PCR	Houston, USA	Open autopsy
Craver R, 2020 Journal 10.1080/15513815.2020.1761491 No mention of the funding source[21]	1	1 M aged 17 years	Intra-hospital	Nasopharyngeal swab	New Orleans, USA	Open autopsy
Aguiar D, 2020 Journal 10.1007/s00414-020-02318-9 No mention of the funding source[22]	1	1 F aged 31 years	Extra-hospital	RT-PCR	Geneva, Switzerland	Open autopsy
Tombolini A, 2020 Journal 10.1007/s00414-020-02354-5 No mention of the funding source[23]	2	2 F aged 64 years	Extra-hospital	RT-PCR	Macerata, Italy	Open autopsy
Wang C, 2020 Journal 10.1016/j.ebiom.2020.102833 Shanghai Guangci Translational Medical Research Development Foundation[24]	2	1 M aged 62 years 1 F aged 53 years	Intra-hospital	RT-PCR	Wuhan and Shanghai, China	Open autopsy
Popa MF, 2020 Journal 10.4323/rjlm.2020.1 No mention of the funding source[25]	1	1 M aged 88 years	Extra-hospital	RT-PCR	Constanta, Rumania	Open autopsy
Fitzek A, 2020 Journal 10.1007/s00194-020-00401-4. No mention of the funding source [12] Heinrich, 2020 Journal 10.1007/s00428-020-02872-y No mention of the funding source[11]	1	1 M aged 59 years	Intra-hospital	RT-PCR	German patient who died in Egypt. Autopsy in Germany	Open autopsy

Author, peer-reviewed or preprint journal, DOI, and source of funding	Number of patients	Participants included	Place of death	Diagnostic method	City, country	Sample collection
Bösmüller H, 2020 Journal 10.1007/s00428-020-02881-x No funding[26]	4	3M, 1 F Average age 72 years	Intra-hospital	RT-PCR	Tübingen, Germany	Open autopsy
Xu Z, 2020 Journal 10.1016/S2213-2600 (20)30076-X No mention of the funding source[27]	1	1M aged 50 years	Intra-hospital	RT-PCR	Beijing, China	Open autopsy
Barton LM, 2020 Journal 10.1093/AJCP/AQAA062[28]	2	1 M aged 42 years 1 M aged 77 years	Extra-hospital	RT-PCR	Oklahoma, USA	Open autopsy
Aiolfi A, 2020 Journal 10.1097/MD.0000000000021046 No funding[29]	2	1 M aged 56 years 1 M aged 70 years	1 intra-hospital 1 no fallecido	Nasopharyngeal swab	Milan, Italy	Thoracoscopic biopsy for resection
Leth PM, 2020 Journal Link: https://ugeskriftet.dk/videnskab/post-mortem-ct-og-obduktion-hos-en-53-arig-mand-med-covid-19 No funding[30]	1	1 M aged 53 years	It is not clear	Positive test	Odense, Denmark	Open autopsy
Magro C, 2020 Journal 10.1016/j.trsl.2020.04.007 No funding[31]	2	1 M aged 62 years 1M aged 73 years	Intra-hospital	RT-PCR	New York and Ohio, USA	Open autopsy limitada
Shao C, 2020 Journal 10.1016/j.humpath.2020.04.015[32]	1	1 M aged 65 years	Intra-hospital	RT-PCR	Beijing, China	Biopsy
Grimes Z, 2020 Journal 10.1016/j.humpath.2020.04.015 No mention of the funding source[33]	2	2 middle-aged M	Intra-hospital	RT-PCR	New York, USA	Open autopsy
Varga Z, 2020 Journal 10.1016/S0140-6736(20)30937-5 No mention of the funding source[35]	3	2 M and 1 F, average age 66 years	Intra-hospital	Not mentioned	Zurich, Switzerland and Boston, USA	Open autopsy
Okudela K, 2020 Journal 10.1111/pin.13002 No mention of the funding source[36]	1	1 F aged 94 years	Intra-hospital	RT-PCR	Kanagawa, Japan	Open autopsy
Navarro Conde P, 2020 Journal 10.1016/j.patol.2020.04.002 No mention of the funding source[37]	1	1 M aged 69 years	Intra-hospital	Descarte de otros virus	Valencia, Spain	Open autopsy
Ducloyer M, 2020 Journal 10.1007/s00414-020-02390- No mention of the funding source[38]	1	1 M aged 75 years	Intra-hospital	RT-PCR	Nantes and Lyon, France	Open autopsy
Wagner WL, 2020 Journal 10.1007/s00117-020-00743-w. No mention of the funding source[39]	2	1 M aged 71 years 1 M aged 76 years	Intra-hospital	RT-PCR	Heidelberg and Gôttinguen, Germany	Open autopsy
Oprinca GK, 2020 Journal 10.1007/s00414-020-02406-w No mention of the funding source[40]	3	1 F aged 79 years 1 M aged 27 years 1 M aged 70 years	2 intra-hospital 1 extra hospitalaria	Not mentioned	Sibiu, Rumania	Open autopsy
Cirstea A-E, 2020 Journal 10.47162/RJME.61.1.23 No mention of the funding source[41]	1	1 F aged 30 years	Extra-hospital	RT-PCR	Bucarest, Rumania	Open autopsy
Dettmeyer R, 2020 Journal 10.1007/s00194-020-00408-x No funding[42]	3	3 men aged 59 to 67 years	2 intra-hospital 1 extra-hospital	Not mentioned	Gleben, Germany	Open autopsy

Author, peer-reviewed or preprint journal, DOI, and source of funding	Number of patients	Participants included	Place of death	Diagnostic method	City, country	Sample collection
Bidari Zerehpoosh F,2021 Journal 10.34172/aim.2021.23 No mention of the funding source[43]	5	1 F aged 78 years 1 F aged 75 years 1 F aged 47 years 1 M aged 48 years 1 M aged 75	Intra-hospital	3 by RT-PCR 1 by CT 1 by CXR	Teheran, Iran	Open autopsy
The COVID-19 autopsy project, 2021 Journal 10.1016/j.patol.2020.05.004 Funded by Carlos III Health Institute, CIBERONC and European Development Regional Fund[45]	1	1 M aged 54 years	Intra-hospital	RT-PCR	Madrid, Spain	Open autopsy
Khaba MC, 2021 Journal 10.1016/ijid.2020.09.1435 No funding[44]	1	1 M aged 19 years HIV positive	Intra-hospital	RT-PCR	Pretoria, South Africa	Open autopsy
Takahashi K, 2021 Journal 10.1002/rcr2.724 No mention of the funding source[46]	1	1 M aged 82 years	Intra-hospital	RT-PCR	Okinawa, Japan	Percutaneous needle biopsy
Pernazza A, 2021 Journal 10.1007/s00428-020-02829-1 No mention of the funding source[47]	1	1 M aged 61 years	Not deceased	RT-PCR	Rome, Italy	Surgical biopsy
Zhang H, 2020 Journal 10.7326/M20-0533 Funded by National Natural Science Foundation of China[48]	1	1 M aged 72 years	Intra-hospital	RT-PCR	Wuhan, China	Percutaneous needle biopsy

M: male, F: female, Rt-PCR: Reverse-transcription polymerase chain reaction, CXR: Chest X radiography CT: Computed tomography.

also recorded reasons for excluding some studies at any stage of the search and the selection process. They mapped out the study selection process in a flow chart adapted to the purpose of the study.

Data collection process

A standardized Excel format was used to include study data. The information to collect was as follows: primary and secondary data, study design, publication status, setting (location/country where autopsies were performed), number of subjects included, numbers of subjects with histological examination of lung tissue, the source of funding, disclosure of conflicts by investigators, a diagnostic method for COVID-19, method for retrieving specimens for histological examination; and data to assess the risk of bias for each study. Disagreements were solved by discussion and article data verification, and an author referee adjudicated unresolved ones.

Data elements

The results were presented in frequencies for each distinguishable finding, describe as a histologic morphologic findings per subject in each study. The frequencies extracted from each study from different presentations such as summary tables and detailed descriptions with findings photographs. A pathology specialist reviewed finding descriptions and designations to summarize similar morphological ones appropriately and without error.

The articles that did not include the number of subjects in whom any morphological change occurred were assumed to be present in all of them.

Risk of bias assessment

Four reviewers made independent assessments of the risk of bias for each study. The critical evaluation tool created by the Joanna Briggs Institute (two reviewers for case series and two reviewers and case reports)[10]. The responses to the guiding questions and the collective supporting information led to a domain-level judgment in the form of "low risk of bias," "some doubt," "unclear," and "high risk of bias." Differences among the reviewers were solved through discussion until a reached consensus. When necessary, a third reviewer resolved discrepancies.

Measurements

Each morphologic change was at the specific lung histologic level. Moreover, it was counted and presented as a single frequency for each study.

Synthesis method

The total frequencies of findings for each study were summaries in frequencies. Then, the overall proportions were from the total number of subjects as a reference (594). Subsequently, a meta-analysis of proportions was performed for two most frequent histologic findings using the free software environment for R statistical computing with a random effects model with the DerSimonian-Liard method. The overall proportion is with its respective 95 % confidence interval. Heterogeneity was estimated using the statistic I^2. A sensitivity analysis in which reports considered to be at "high risk of bias" was eliminated from the meta-analysis.

Results

A total of 252 references were on the L·OVE platform and 170 on PubMed and other searches. After verifying the titles, abstracts, and duplicates, 185 studies were selected for potential inclusion. Articles that reported histological findings in organs other than lungs were detached, as well as those on only biosafety measures for autopsies. Then, 116 articles were excluded, leaving 69 for inclusion, with 595 subjects. Two articles were found that reported findings from the same subject[11,12]. Finally, a total was 594 subjects. It is in the PRISMA flow chart (Figure 1).

Characteristics of the studies

Among 69 included studies, 38 were case reports[11- 48] and 31 were case series[3-5,49-76]. Among included articles, 67 were in peer-reviewed journals, and two were in preprints. Peer-reviewed journals and two were in preprints. The demographic characteristics were: 381 males,179 females, and 34 did not specify the sex of the subjects. The mean age for the case series was 87.57 years ± SD 1.57, and for the case, the report was 61.85 years ± SD 1.51. The studies were performed in eleven countries, mainly the United States (Table 1).

The findings reported: a total of 461 in-hospital deaths, 29 out-of-hospital, three non-deaths, 104 were unclear, and one was not reported.

Regarding diagnostic tests for confirmation of COVID-19, a nasopharyngeal swab was in 81 patients. There was mention in six of how they had confirmed the diagnosis, one by ruling out many respiratory viruses, one by computed tomography, and one by chest X-ray (Table 1).

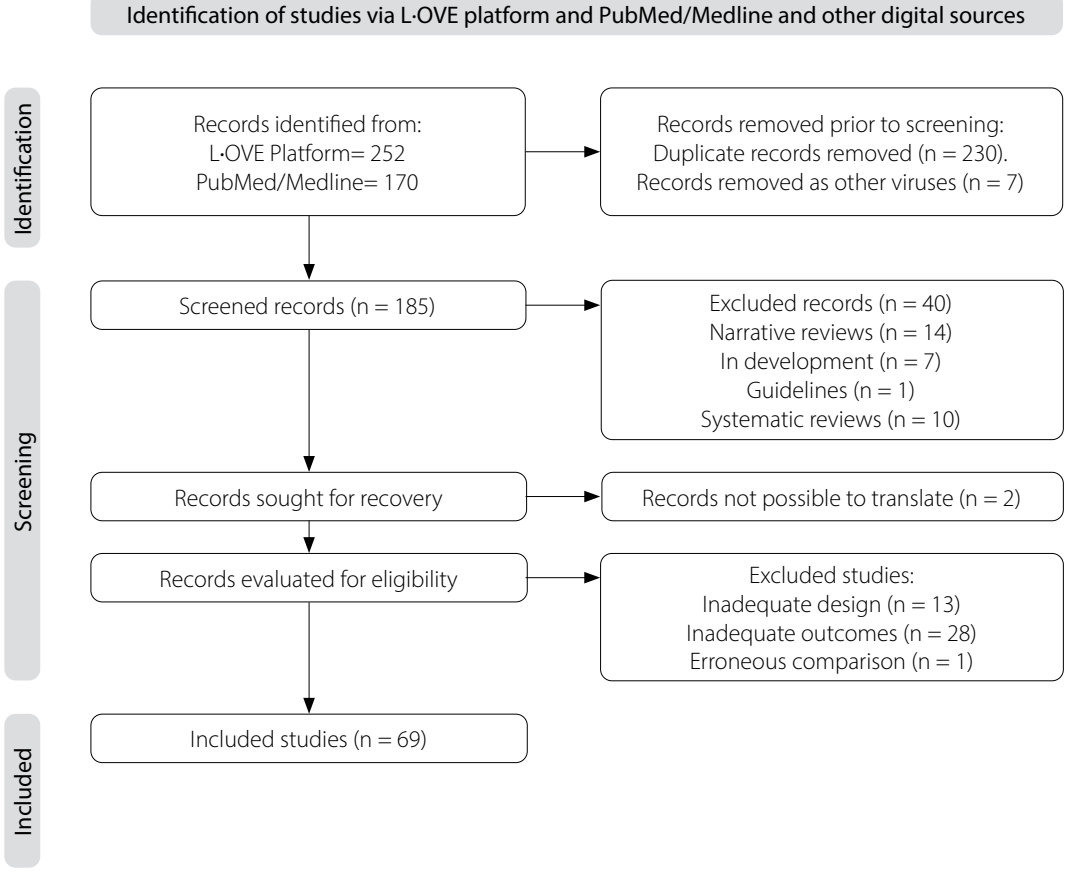

Figure 1. PRISMA flowchart of included studies

The specimens for histological examination were recovered from open autopsies, but there were open autopsies, but there were descriptions of modalities such as ten percutaneous biopsies ultrasonography-guided percutaneous biopsies, three surgical biopsies and two thoracoscopies (Table 1). All samples were stained with hematoxylin and eosin and examined with and eosin, examined with regular and electron microscopy and were and electron microscopy, and immunohistochemical immunohistochemistry tests.

Risk of bias in studies

Case series: 14 articles (41.36 %) were as "low risk of bias" of which six had control of the ten risks of bias required for case series assessment (19.35 %), and eight with control of nine of the risk of bias. The bias of "mention of inclusion criteria" was absent in five articles but it was unclear in ten articles. The most frequently uncontrolled bias was "adequate statistical processing of data" in 19 of the series (61.29 %). The bias that was 100 % controlled was the "clear reporting of the study outcome", followed by the bias of "clear reporting of the demographic characteristics of the subjects included in the series" and "clear reporting of the clinical information of the subjects included" in 90 % each.
Case reports: Twenty-nine articles assessed as "low risk of bias" (76.31 %), of which 20 met the seven risk of bias control requirements for case reports, and nine met six requirements. The two biases that were 100 % controlled were "clear reporting of outcome" and "the article teaches a lesson" followed by the bias "patient history was presented and used as a baseline over time" at 90 %.

Histopathological morphological findings

The most common finding by single frequency was diffuse alveolar damage (DAD) in 323 cases (55.72 %). In 275 cases, there were early components of platelet fibrin thrombi, hyaline membranes, and edema (85.14 %), followed by any arterial thrombosis (microthrombosis and macrothrombosis) in 271 cases: 252 microthrombosis and 231 macrothrombosis, of which in 19 cases of macrothrombosis identified were not in conjunction with microthrombosis. In 117 subjects presenting with any arterial thrombosis, no DAD was described equivalent to 43.17 % of all subjects with thrombosis (Table 2).

The data obtained by meta-analysis of proportions were 0.62 for DAD (95 % CI 0.51- 0.72), I^2 heterogeneity 59 % ($p < 0.01$), and 0.40 for any arterial thrombosis (95 % CI 0.31- 0.49), I^2 heterogeneity 58 % ($p < 0.01$) (Figures 2 and 3).

There was a sensitivity analysis and a removing all articles with at least one high-risk factor for bias. DAD was 0.65 (95 % CI 0.54 - 0.76), I^2 heterogeneity 59 % ($p < 0.01$), and 0.43 with any type thrombosis (95 % CI 0.33 - 0.54), I^2 heterogeneity 62 % ($p < 0.01$).

A sensitivity analysis was performed; all articles with at least one high-risk factor for bias were removed; 0.65 was for DAD (95 % CI 0.5 4 -0.76), heterogeneity I^2 62 % ($p < 0,01$).

Discussion

This systematic review achieved to summarize histological findings retrieved from lung specimens in COVID-19 patients through a new rapid and sensitive search technology, the L·OVE platform on the Epistemonikos database. Most of the findings came from patients who had died, either in or out of hospital, and patients from whom samples were taken during their lifetime who subsequently died. At the beginning of the pandemic, results were slow because of the extreme precautions taken in pathology due to the contagious nature of the disease. However, when autopsies report could be performed safely, publications increased.

By the end of 2020, many articles that had been published in "preprint" format were later published in peer-reviewed journals, except for two that even at the time of finalizing this paper were still as preprint and therefore not peer-reviewed.

The literature currently available on lung histologic findings in COVID-19 patients is heterogeneous, as each publication responds to different objectives: To support theories for the cause of respiratory failure and cause of death[5,54,56]; for being the first autopsy report on COVID-19 patient made in the country or region[11,37,45]; undiagnosed home deaths but with previous suggestive symptoms or to add findings, such as being young, dying in another country or other relevant finding[11,12]. It generated a limitation to this study since it introduces a selection bias as the cases were "chosen" by the authors. The other limitation was the definition of COVID-19. Not all included subjects were diagnosed using Rt-PCR, pre or *post mortem*. There was one case autopsied as excluded due to the presence of other viruses. But even with these limitations, this review shed light on many concerns about the cause of respiratory failure. Although some findings were described, which in many cases could

Table 2. Individualized histological findings, their frequencies and percentages

Morphologic histological findings	Frequencies (%)
Total number of cases	594
Diffuse alveolar damage	323 (54.37)
Isolated morphological characteristics of DAD	
Acute phase Exudative	
Hyaline membrane	275 (46.29)
Interstitial and intra-alveolar edema	151 (25.42)
Capillary congestion	125 (21.04)
Alveolar hemorrhage	124 (20.87)
Platelet fibrin thrombi	109 (18.35)
Fibrinous exudate	63 (10.60)
Endothelial necrosis	45 (7.57)
Loss of pneumocytes	45 (7.57)
Dissociation of pneumocytes from basement membrane forming a pattern of desquamation	40 (6.73)
Proliferative/Organization (subacute phase)	
Pneumocytic hyperplasia type 2	240 (40.40)
Diffuse interstitial lymphocytic infiltrate	147 (24.74)
Deposition/proliferation of septal collagen	101 (17.0)
Organized/collapsed alveoli with ductal dilatation	86 (14.48)
Interstitial myofibroblastic reaction	65 (10.94)
Alveolar granulocytes	45 (7.57)
Enlarged megakaryocytes	44 (7.41)
Intra alveolar fibrin 36	36 (6.06)
Intra alveolar macrophage	29 (4.88)
Perivascular compression and lymphocytic vasculitis	24 (4.04)
Interstitial proliferation	8 (1.35)
Intra alveolar lymphocytic infiltrate	5 (0.84)
Fibrotic (chronic phase)	
Fibrosis	48 (8.08)
Thrombotic morphological changes	
Micro thrombosis in small and medium diameter arteries	252 (42.42)
Pulmonary artery thrombosis	196 (32.99)
Peripheral pulmonary embolism	35 (5.89)
Pulmonary vessel endothelial damage	28 (4.71)
Intra alveolar micro thrombosis	11 (1.85)
Other morphological findings	
Intra-alveolar pneumocytes forming aggregates similar to giant multinucleated cells suspicious of cytopathic viral effect	113 (19.02)
Suppurative pneumonia	62 (10.44)
Squamous metaplasia	17 (2.86)
Amyloid in pulmonary vessels	11 (1.85)
Extensive *Corporae amylacea*	7 (1.18)
Increased density of angiogenic intussuceptive features	7 (1.18)
Pleural adhesions	7 (1.18)
Mucinous secretion in bronchioles and bronchial mucus plugs	6 (1.01)
Heme-phagocytic histiocytosis in the pulmonary hilum	5 (0.84)
Syncytial multinucleated cells	2 (0.34)
Eosinophilic infiltrate	2 (0.34)
Intraalveolar mucus	2 (0.34)
Acute pneumonitis	1 (0.16)
Multicavitary lesions	1 (0.16)
Pleural effusion	1 (0.16)
Lymphocytic pleuritis	1 (0.16)

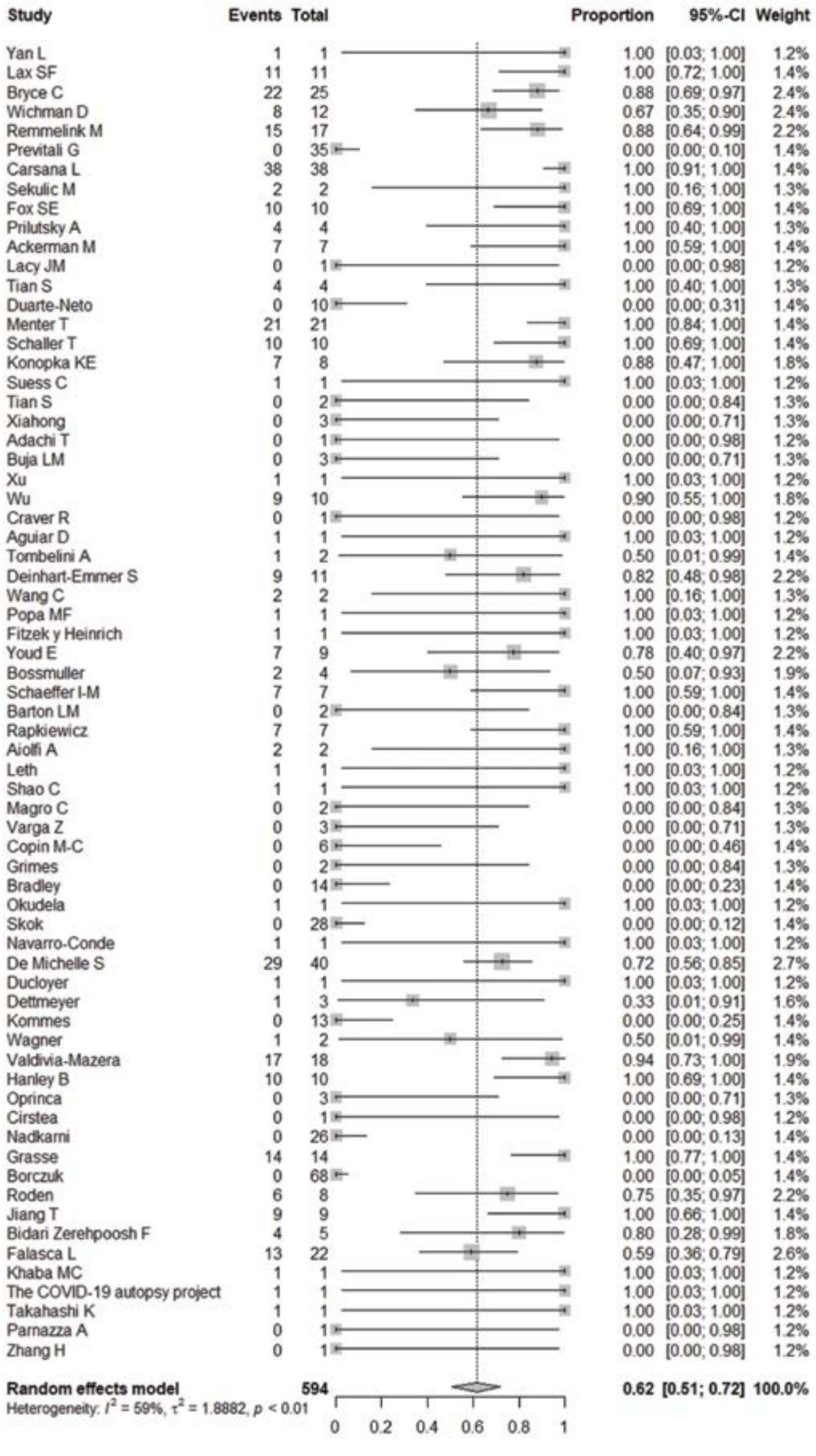

Figure 2. Meta-analysis forest plot for proportions of diffuse alveolar damage

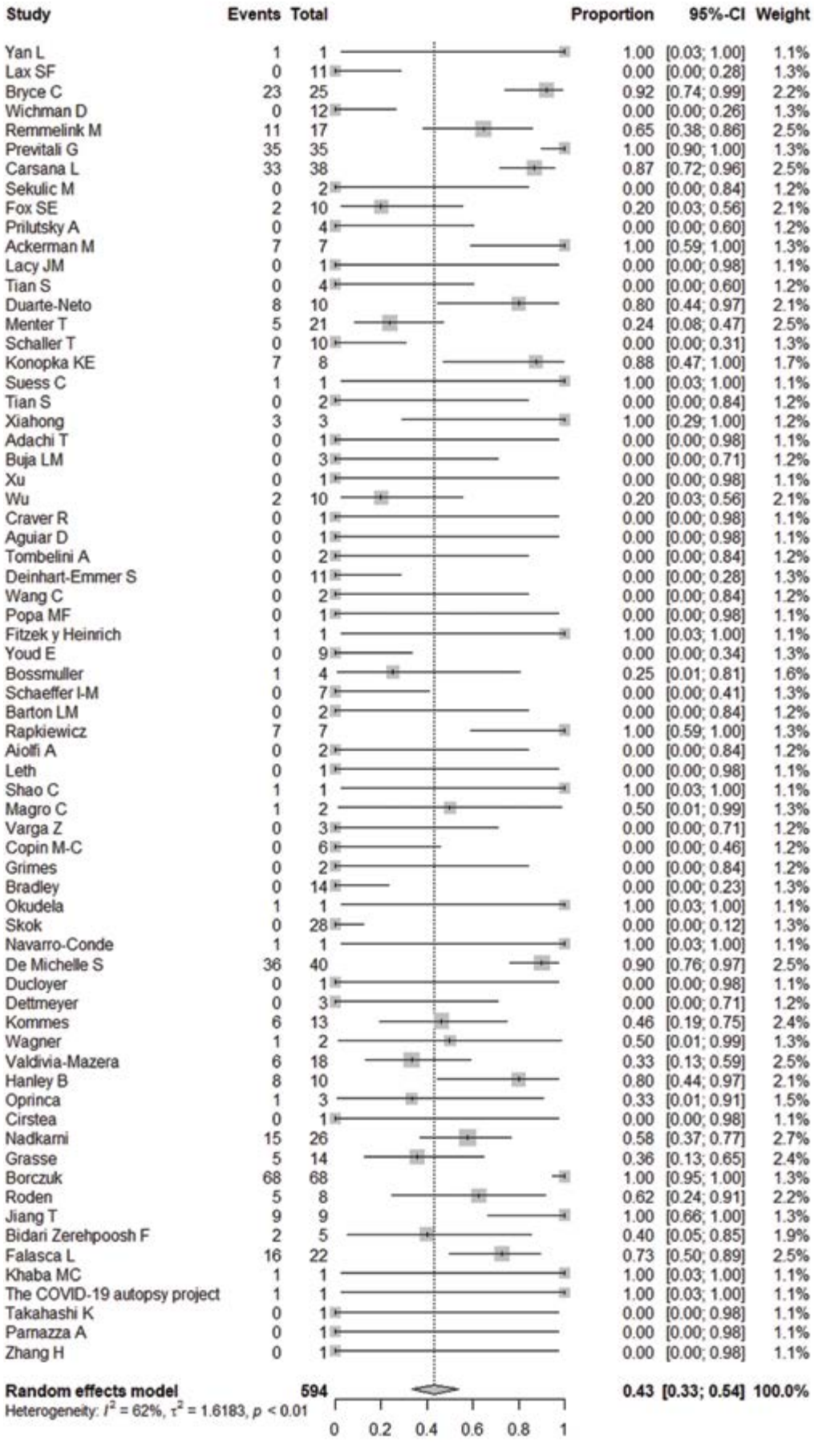

Figure 3. Meta-analysis forest plot for proportions of any arterial thrombosis

have occurred due to underlying causes of the subjects, the most frequent was DAD in all its stages. It is a morphologic feature that accompanies acute respiratory distress syndrome, regardless of its origin. However, the frequent finding of morphological alterations in early stages of DAD, with its typical hyaline membranes, intra-alveolar platelets and fibrin thrombi and edema, at the time of death and not in the stages of consolidation towards fibrosis as in acute fibrinous and organized pneumonia, reported in six autopsy cases,[54] should be emphasized. It is also important to note that there were no differences between patients who died at home and those who died of respiratory failure on mechanical ventilation. Regarding the theory of hypercoagulability that led many clinicians to use high-dose heparins and give aspirin, there is also no difference in its increased presence in critically ill patients.

These findings can guide clinical practice to the aggressive anticoagulation proposed at one time in disease management and the fact of finding few concomitant bacterial infections and thus making rational use of antibiotics in these patients. There is still much to learn about this disease, especially since new variants appear, and the clinical behavior and systemic involvement may also vary. Most of these reports are from the initial variant.

Conclusions

The most frequent histological morphological change are diffuse alveolar damage, indistinct from those produced by different viral infections. There was no finding of a specific pathognomonic characteristic that diagnoses COVID-19.

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