Extrapulmonary CT Findings Predict In-Hospital Mortality in COVID-19. A Systematic Review and Meta-Analysis

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Rationale and Objectives: Several prognostic factors have been identified for COVID-19 disease. Our aim was to elucidate the influence of non-pulmonary findings of thoracic computed tomography (CT) on unfavorable outcomes and in-hospital mortality in COVID-19 patients based on a large patient sample.

Materials and Methods: MEDLINE library, Cochrane and SCOPUS databases were screened for the associations between CT-defined features and mortality in COVID-19 patients up to June 2021. In total, 22 studies were suitable for the analysis, and included into the present analysis. Overall, data regarding 4 extrapulmonary findings could be pooled: pleural effusion, pericardial effusion, mediastinal lymphadenopathy, and coronary calcification.

Results: The included studies comprised 7859 patients. The pooled odds ratios for the effect of the identified extrapulmonary findings on in-hospital mortality are as follows: pleural effusion, 4.60 (95% CI 2.97-7.12); pericardial effusion, 1.29 (95% CI 0.83-1.98); coronary calcification, 2.68 (95% CI 1.78-4.04); mediastinal lymphadenopathy, 2.02 (95% CI 1.18-3.45).

Conclusion: Pleural effusion, mediastinal lymphadenopathy and coronary calcification have a relevant association with in-hospital mortality in COVID-19 patients and should be included as prognostic biomarker into clinical routine.

Key Words: Meta analysis; Systematic review; CT; COVID-19.

RATIONALE AND OBJECTIVES

The prevalent coronavirus disease 2019 (COVID-19) pandemic has spread throughout the world and is considered a serious threat to global health.

The clinical course of COVID-19 is highly variable. Early during the pandemic, it was identified that most patients have a mild disease course with little or even no symptoms, but a minority of patients rapidly deteriorates to a severe or critical illness with need of admission to an intensive care unit, and even a fatal outcome (1-4). The case fatality rate during the first peak of the pandemic was over 10% in most European countries (2). Therefore, prediction of unfavorable courses of COVID-19 can be crucial for patient care, especially during early stages of the disease (2).

Already established prognostic factors are age and sex with the reported hazard ratios of 2.6 for age over 60 years and 1.4 for male sex (5,6). Moreover, a shorter time period between symptom onset and emergency room presentation is also a prognostic factor (2). Comorbidities including dementia, heart failure, and peripheral vascular diseases are also predictors of an unfavourable course of the disease (6).

Computed tomography (CT) is the diagnostic imaging modality of choice in COVID-19, especially for detection of pulmonary consolidations (2,7,8). In cases suspicious for COVID-19, it can be acquired without administration of contrast media, and in low-dose technique (7). Typical imaging findings of COVID-19 were already reported in the early stages of the pandemic (4). The pulmonary consolidations were described as bilateral, peripheral dominant ground-glass opacities with lower lobe, and posterior predilection (7).

Extrapulmonary findings, comprising pleural effusion, pericardial effusion, mediastinal lymphadenopathy, were described as atypical, and should raise the concerns for

possible differential diagnoses (7). However, there were published data, that even these rare findings in COVID-19 patients exist, and can predict a more severe or lethal course of the disease (9).

Since the early days of the pandemic, the introduction of vaccination has changed the course of the pandemic, but lethal COVID-19 cases still exist, and correct diagnosis and treatment are still highly relevant throughout different countries (10-12).

Early prediction of an unfavourable course of COVID-19 cases is important to improve clinical treatment, such as appropriate triaging, if needed, early admission to ICU, and expanding more aggressive treatment, e.g. with extracorporal membrane oxygenation.

The purpose of the present systematic review and meta-analysis was to calculate the impact of CT-derived extrapulmonary features with in-hospital mortality in COVID-19 patients.

METHODS

Data Acquisition

MEDLINE library, Cochrane and SCOPUS databases were screened for CT findings and in-hospital mortality in COVID-19 patients up to June 2021. The paper acquisition is summarized in Figure 1.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used for the analysis (13).

The studies were screened for potential prognostic CT findings. Most studies reported prognostic relevance of pleural effusion, pericardial effusion, mediastinal lymphadenopathy, and coronary calcification. These findings were used for further analyses.

The following search words were used: "COVID-19″ AND "Computed Tomography" OR "CT" AND "mortality" OR "severe course" OR "death."

The primary endpoint of the systematic review was the odds ratio of CT findings on mortality.

Studies (or subsets of studies) were included if they satisfied the following criteria: (1)

COVID-19 diagnosis by PCR-RT, (2) reported CT findings (3) reported odds ratio or hazard ratio with confidence interval (CI). Exclusion criteria were (1) systematic reviews, (2) case reports, (3) non-English language, (4) other imaging modalities than CT.

In total, 22 studies were suitable for the analysis, and included into the present study (14-35).

Data Extraction

Data extraction was performed by HJM followed by an independent evaluation of extractions for correctness (AS). For each study, details regarding study design, year of publication, country of origin, patient number, patient characteristics (age and sex), diagnosis, treatment, CT findings, timepoint of the CT acquisition, survival outcome results, and adjustment factors were extracted.

Quality Assessment

The quality of the included studies was assessed by the Newcastle-Ottawa Scale (NOS) (36). Study quality assessment was conducted by two authors (HJM, AS), and mainly included the selection of cases, comparability of the cohort, and outcome assessment of exposure to risks. A score of $0-9$ was assigned to each study, and a study with score ≥ 6 was considered to be of high quality.

Statistical Analysis

The meta-analysis was performed using RevMan 5.3 (2014; Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was calculated by means of the inconsistency index I^2 (37,38). DerSimonian and Laird random-effect models with inverse variance weights were performed without any further correction (39). Possible publication bias was assessed with funnel plot and Egger test.

Additionally, sub-analyses were performed to test possible heterogeneities caused by different CT techniques (16 slices vs 128 and 256 slices), and by the origin of the studies.

RESULTS

Quality of The Included Studies

Of the included 22 studies, 21 were retrospective (95.4%), and one was prospective (4.6%) (20). Table 1 gives an overview of the included articles.

The overall risk of bias can be considered as low, indicated by the high NOS values among the studies ranging from 5 to 8 points (Table 2). Two studies (15,25) did not report the exact patient recruitment duration, which can result in a potential bias. The exact CT timing was not reported sufficiently in several studies, which can be another bias. Funnel plot displays a publication bias (Fig 2).

Patients

The included studies comprised 7859 patients. There were 4713 men (60%) and 3146 women (40%), with a mean age of 59.6 years ranging from 44.2 to 70 years. In all studies, COVID-19 was diagnosed with RT-PCR.

Overall, 19 studies (86.4%) investigated patients during the first wave of the pandemic, two studies (9.1%) did not report the exact time-period (15,25). Most studies investigated patients between March and April 2020. Only one study analyzed cases after the first wave with inclusion of patients between September and October 2020 (14).

In 15 studies (68.2%) performed CT at the presentation of the admission or within 24 hours after admission. In 6 studies
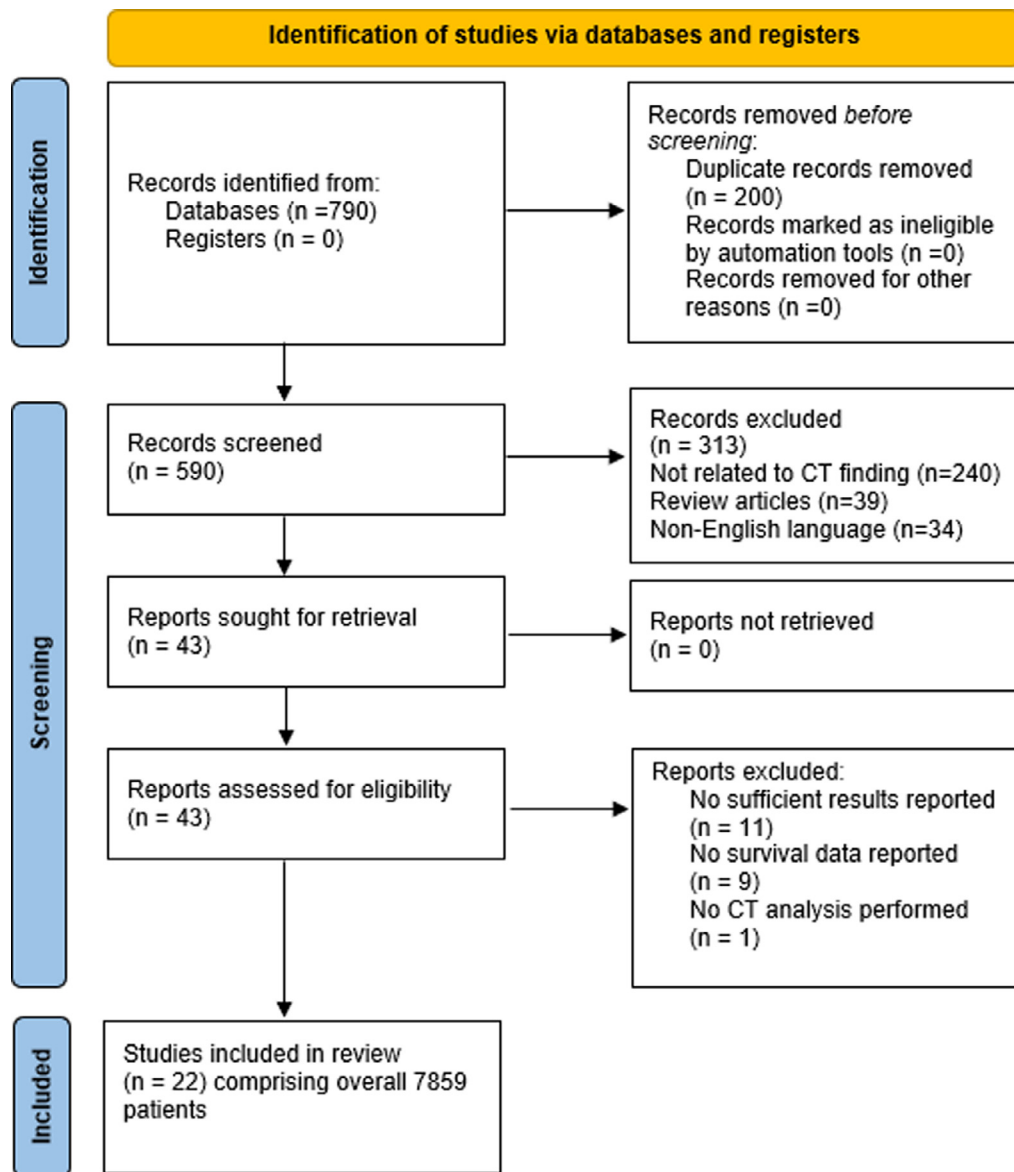
Figure 1. PRISMA flow chart provides an overview of the paper acquisition. Overall, 22 studies with 7859 COVID-19 patients were suitable for the analysis. (Color version of figure is available online.)

(27.3%) the timepoint of the CT was not clearly stated within the manuscript. In one study (30) investigating coronary calcifications, CTs of the patients were included up to 5 years prior to admission.

Thirteen studies (59.1%) were performed in Asia, six studies (27.3%) in Europe, and three studies (13.6%) in North America. Table 3 provides an overview of the investigated sub-analyses according to study origin.

Pleural Effusion

Overall, 15 studies with 3623 patients analyzed the effect of pleural effusion on in-hospital mortality in COVID-19 patients. The pooled odds ratio for the association between pleural

effusion and in-hospital mortality was 4.6 (95% CI 2.97-7.12) (Fig3a).

On the next step, the reported data were analysed in accordance on study origin. Three studies with 772 patients were performed in Europe. The pooled odds ratio was 5.89 (95% CI 1.83-18.94) (Fig 3b). Two studies with 1303 patients were performed in China. The pooled odds ratio was 15.04 (95% CI 3.72-60.82) (Fig 3c). Finally, eight studies with 1158 patients were performed in Iran. The pooled odds ratio was 3.43 (95% CI 1.96-5.99) (Fig 3d).

Also, a sub-analysis of the data according to the used CT scanners was performed.

In seven studies with 1184 patients, 16 slices CT scanners were used. The pooled odds ratio was 5.26 (95% CI 2.62-10.56) (Fig 3e). In two studies with 757 patients, 128 or 256

TABLE 1. Overview of the Included Studies

Authors	Country	Study design	Time period of the study	Mean age, years	Gender, female, n (%)	Included patients, n	Patients with CT-finding, n (%)	CT scanner	Time frame of CT acquisition
Abkhoo et al., 2021	Iran	Retrospective	September-October 2020	62.2	39 (32.2)	121	30 (24.8) pleural effusion, 13 (10.7) pericardial effusion	6-16 slices	Chest CT at base line
Abrishami et al., 2020	Iran	Retrospective	Unclear	60.6	15 (34.9)	43	9 (20.9) pleural effusion 29 (8) mediastinal lymphadenopathy (unclear threshold)	64-slices	Chest CT with unclear timing
Ashtari et al., 2021	Iran	Retrospective	March -April 2020	61.6	95 (26.2)	363	41 (11.3) pleural effusion	16-slices	Chest CT at base line
Chon et al., 2020	South Korea	Retrospective	February 22-April 3 2020	61.5	206 (73.3)	281	13 (4.6) pleural effusion	128-slices	Chest CT at base line
Eslami et al., 2020	Iran	Retrospective	February 20-April 10 2020	54.5	30 (35.5)	87	15 (17.2) Pericardial effusion	64-slices	Chest CT at base line
Giannini et al., 2021	Italy	Retrospective	March 1-April 20 2020	68	352 (31.7)	1093	734 (67.2) coronary calcification	Different scanner, 16-128 slices	Chest CT at base line
Grodecki et al., 2021	USA	Prospective	January 10-April 14 2020	64	41 (38)	109	15 (13.8) pleural effusion	Different scanner, 16-128 slices	Chest CT at base line
Gupta et al., 2021	USA	Retrospective	March 1-April 27 2020	68	82 (46)	180	129 (71.7) coronary calcification	Different scanner 64-256 slices	Chest CT at base line
Khosravi et al., 2021	Iran	Retrospective	February 18-April 19 2020	43% of patients over 65 years	54 (44.6)	121	26 (21.7) pleural effusion 18 (14.9) pericardial effusion 6 (5) mediastinal lymphadenopathy (>10 mm)	16-slices	Chest CT at base line
Meiler et al., 2020	Germany	Retrospective	March 1-April 15 2020	57.2	24 (38)	64	13 (20) pleural effusion 18 (28) mediastinal lymphadenopathy (> 10 mm)	16 and 128- slices	Chest CT at base line, 20% with contrast media

TABLE 1. (Continued)

Authors	Country	Study design	Time period of the study	Mean age, years	Gender, female, n (%)	Included patients, n	Patients with CT-finding, n (%)	CT scanner	Time frame of CT acquisition
Mozafari et al., 2021	Iran	Retrospective	February 29-April 3 2020	50.6	100 (46.9)	213	7 (3.3) pleural effusion	16-slices	Chest CT at base line
Mruk et al., 2021	Poland	Retrospective	Unclear	56.7	67 (42.9)	156	12 (7.7) pleural effusion 12 (7.7.) mediastinal lymphadenopathy (> 10 mm)	16-slices	Chest CT at base line
Satici et al., 2021	Turkey	Retrospective	April 2-May 15 2020	56.9	317 (49.8)	650	60 (9.2) mediastinal lymphadenopathy (> 10 mm)	128-slices	Chest CT at base line
Sattarzadeh Badkoubeh et al., 2021	Iran	Retrospective	March 5-March 27 2020	58.8	34 (39.5)	86	5 (5.8) pericardial effusion	Unclear	Chest CT with unclear timing
Schiaffino et al., 2021	Italy	Retrospective	February 21-April 30 2020	65	188 (34)	552	39 (7) pleural effusion 87 (16) mediastinal lymphadenopathy (> 10 mm)	Different scanners 16-128 slices	Chest CT within 24 h of admission
Scoccia et al., 2021	Italy	Retrospective	March 1-April 24 2020	69	533 (32.8)	1625	1121 (69.0) coronary calcification	Different scanner, at least 16 slices	Chest CT with unclear timing
Slipszuk et al., 2021	USA	Retrospective	March 1-June 26 2020	70	249 (51.5)	493	308 (67.7) coronary calcification	Different scanners 16-128 slices	Chest CT during or 5 years prior to admission
Tabatabaei et al., 2020	Iran	Retrospective	February 20-March 2 2020	54.9	50 (41.7)	120	20 (16.7) pleural effusion	16-slices	Chest CT at baseline
Tabatabaei et al., 2020	Iran	Retrospective	February 20-April 19 2020	44.2	36 (40)	30 deceased patients with 60 matched controls	14 (15.6) pleural effusion	16-slices	Chest CT with unclear timing
Wei et al., 2021	China	Retrospective	January 20-February 29 2020	50.9	376 (45.5)	827	76 (9.2) pleural effusion	Unclear	Chest CT with unclear timing
Zhan et al., 2021	China	Retrospective	January 20-March 23 2020	62.3	223 (46.8)	476	153 (32.1) pleural effusion	64-slices	Chest CT at baseline
Zimmermann et al., 2020	Germany	Retrospective	March 5-April 15 2020	61.8	35 (32.1)	109	69 (63.3) coronary calcifications	64 and 256 slices	Chest CT with unclear timing

Abbreviations: CT, Computed tomography.

TABLE 2. The Quality of the Studies Defined by NOS Scale

Study	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Quality Score
Abkhoo et al., 2021		*	*		*	*	*	*	6
Abrishami et al., 2020		*	*	*		*	*	*	5
Ashtari et al., 2021	*	*	*		*	*	*	*	7
Chon et al., 2020	*	*	*		*	*	*	*	7
Eslami et al., 2020	*	*	*	*	*	*	*	*	8
Giannini et al., 2021	*	*	*	*	*	*	*	*	8
Grodecki et al., 2021	*	*	*	*	*	*	*	*	8
Gupta et al., 2021	*	*	*	*	*	*	*	*	8
Khosravi et al., 2021	*	*	*		*	*	*	*	7
Meiler et al., 2020	*	*	*	*	*	*	*	*	8
Mozafari et al., 2021	*	*	*	*	*	*	*	*	8
Mruk et al., 2021			*	*		*	*	*	5
Satici et al., 2021	*	*	*		*	*	*	*	7
Sattarzadeh Badkoubeh et al., 2021	*	*	*		*	*	*	*	7
Schiaffino et al., 2021	*	*	*	*	*	*	*	*	8
Scoccia et al., 2021	*	*	*	*	*	*	*	*	8
Slipszuk et al., 2021	*	*	*		*	*	*	*	7
Tabatabaei et al., 2020	*	*	*	*	*	*	*	*	8
Tabatabaei et al., 2020	*	*	*	*	*	*	*	*	8
Wei et al., 2021	*	*	*	*	*	*	*	*	8
Zhan et al., 2021	*	*	*		*	*	*	*	7
Zimmermann et al., 2020	*	*	*		*	*	*	*	7

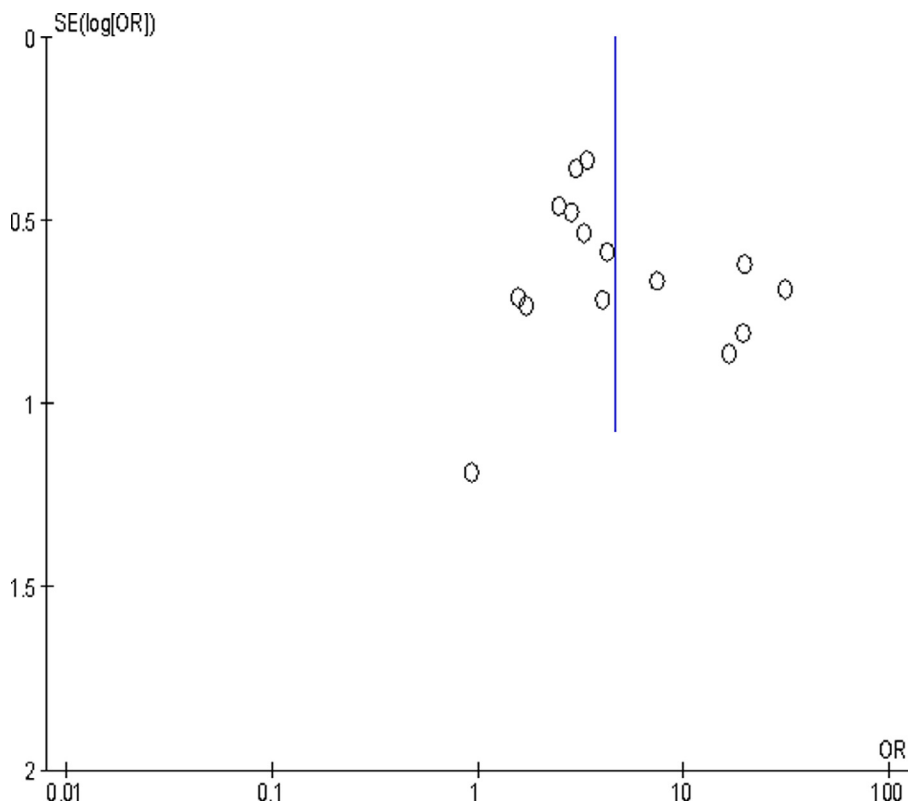Abbreviation: NOS, Newcastle-Ottawa Scale

Figure 2. Funnel plot displays no relevant publication bias. (Color version of figure is available online.)

slices CT scanners were used. The pooled odds ratio was 15.04 (95% CI 3.72–60.82) (Fig 3f).

Pericardial Effusion

In five studies with 1508 patients the effect of pericardial effusion on in-hospital mortality in COVID-19 patients was investigated. The pooled odds ratio for the association between pericardial effusion and mortality was 1.29 (95% CI 0.83–1.98) (Fig 4).

No sub-analyses could be performed for perdicardial effusion.

Coronary Calcification

In five studies (3500 patients) the effect of pericardial effusion on in-hospital mortality in COVID-19 patients was analyzed. The effect of coronary calcification was defined in all studies by presence of calcified plaques. The pooled odds ratio for the association between coronary calcification and mortality was 2.68 (95% CI 1.78-4.04) (Fig 5a).

Overall, three studies with 2827 patients were performed in Europe. The pooled odds ratio was 3.30 (95% CI 2.60-4.20) (Fig 5b). The remaining two studies with 673 patients were performed in the USA. The pooled odds ratio was 2.08 (95% CI 0.88-4.94) (Fig 5c).

Mediastinal Lymphadenopathy

In six investigations with 1906 patients the effect of pericardial effusion on in-hospital mortality in COVID-19 patients was studied. In 5 studies the threshold value of the short axis diameter was 10 mm, in one study (15) no threshold value was provided.

The pooled odds ratio for the association between mediastinal lymphadenopathy and mortality was 2.02 (95% CI 1.18-3.45) (Fig 6a).

Three studies with 772 patients originated from Europe countries. The pooled odds ratio was 2.77 (95% CI 1.12-6.87) (Fig 6b). The remaining two studies with 484 patients were performed in Iran. The pooled odds ratio was 0.94 (95% CI 0.44-2.01) (Fig 6c).

TABLE 3. Overview of the Subanalyses of the Investigated CT Findings According to Study Origin

Origin	Female/male ratio (%)	Mean age in years
Pleural effusion		
Europe	279/493 (36.1)	59.8
China	429/328 (56.7)	61.6
Iran	395/703 (36.0)	56.2
Coronary Calcification		
Europe	866/1750 (33.1)	64.3
USA	331/342 (49.2)	69
Mediastinal Lymphadenopathy		
Europe	279/493 (36.1)	59.3
Iran	149/335 (30.8)	61.0

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DISCUSSION

This is the first meta-analysis regarding associations between non-pulmonary CT findings and mortality in COVID-19 patients. As shown, there was a statistically significant association of pleural effusion, coronary calcifications, and mediastinal lymphadenopathy with in-hospital mortality, whereas no significant association was identified with pericardial effusion. These findings highlight the importance of extrapulmonary findings in COVID-19 infection.

Figure 3. (a) Forrest plots of the odds ratios for the effect of pleural effusion on in-hospital mortality in COVID-19. The pooled odds ratio was 4.6 (95% CI 2.97-7.12). (b) The pooled odds ratio for pleural effusion in the studies from Europe was 5.89 (95% CI 1.83-18.94). (c) The pooled odds ratio for studies from China was 15.04 (95% CI 3.72-60.82). (d) The pooled odds ratio for pleural effusion in the studies from Iran was 3.43 (95% CI 1.96-5.99). (e) The pooled odds ratio for pleural effusion based on the studies used 16-sclice CT scanners was 5.26 (95% CI 2.62-10.56). (f) The pooled odds ratio for pleural effusion based on the studies used 128- and 256-sclice CT scanners was 15.04 (95% CI 3.72-60.82). (Color version of figure is available online.)

(d)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Abkhoo 2021	1.186	0.535	15.4%	3.27 [1.15, 9.34]
Abrishami 2020	-0.064	1.186	4.9%	0.94 [0.09, 9.59]
Ashtari 2021	1.221	0.338	23.0%	3.39 [1.75, 6.58]
Eslami 2021	0.541	0.735	10.4%	1.72 [0.41, 7.25]
Khosravi 2021	0.916	0.46	18.0%	2.50 [1.01, 6.16]
Mozafari 2021	2.808	0.862	8.3%	16.58 [3.06, 89.79]
Tabatabaei 2020a	2.962	0.81	9.1%	19.34 [3.95, 94.59]
Tabatabaei 2020b	0.462	0.71	10.9%	1.59 [0.39, 6.38]
Total (95% CI)			**100.0%**	**3.43 [1.96, 5.99]**

Heterogeneity: Tau^2 = 0.24; Chi^2 = 11.62, df = 7 (P = 0.11); I^2 = 40%
Test for overall effect: Z = 4.33 (P < 0.0001)

favours pleural effusion   no pleural effusion

(e)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Abkhoo 2021	1.186	0.535	15.7%	3.27 [1.15, 9.34]
Ashtari 2021	1.221	0.338	20.0%	3.39 [1.75, 6.58]
Khosravi 2021	0.916	0.46	17.3%	2.50 [1.01, 6.16]
Mozafari 2021	2.808	0.862	10.0%	16.58 [3.06, 89.79]
Mruk 2021	2.978	0.621	14.0%	19.65 [5.82, 66.36]
Tabatabaei 2020a	2.962	0.81	10.7%	19.34 [3.95, 94.59]
Tabatabaei 2020b	0.462	0.71	12.3%	1.59 [0.39, 6.38]
Total (95% CI)			**100.0%**	**5.26 [2.62, 10.56]**

Heterogeneity: Tau^2 = 0.52; Chi^2 = 15.99, df = 6 (P = 0.01); I^2 = 62%
Test for overall effect: Z = 4.67 (P < 0.00001)

favours pleural effusion   no pleural effusion

(f)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Chon 2020	3.435	0.69	49.2%	31.03 [8.03, 119.99]
Zhan 2021	2.009	0.666	50.8%	7.46 [2.02, 27.50]
Total (95% CI)			**100.0%**	**15.04 [3.72, 60.82]**

Heterogeneity: Tau^2 = 0.56; Chi^2 = 2.21, df = 1 (P = 0.14); I^2 = 55%
Test for overall effect: Z = 3.80 (P = 0.0001)

favours pleural effusion   no pleural effusion

Figure 3 Continued.

COVID-19 has a high mortality for patients with an unfavourable course. Thus, a short-term mortality of up to 20% was reported in COVID-19 patients admitted to the intensive care unit (ICU) (2-6,40). As mentioned previously, established prognosis parameters are age above 60 years and male sex, shorter period between symptom onset, and emergency room presentation (2-6,40). Moreover, the extension of pulmonary consolidation on CT images is also considered as prognostic relevant (2,41). The consolidations are indicative of a disease progression and are most prominent in day 10 of the disease (8).

The present analysis highlights the importance of CT for prognostic purposes beyond the quantification of pulmonary consolidations. Notably, the reported odds ratios are good comparable to the established risk factors, such as higher age over 60 years, and male sex (5), which highlights the importance of the extrapulmonary CT findings.

In a recent meta-analysis regarding CT findings in COVID-19, the time dependence of different CT findings was investigated (42). Pleural effusion and lymphadenopathy were more frequently identified in later disease stages (42). So far, pleural effusion was found in 5% of patients in early stages and in 16% of patients in advanced stages (42). Similarly, mediastinal lymphadenopathy was observed in 4% of patients in early stages and in 15% of patients in advanced stages (42). The time dependence may be a potential confounder of the

Figure 4. Forrest plots of the odds ratios for the effect of pericardial effusion on in-hospital mortality in COVID-19. (Color version of figure is available online.)
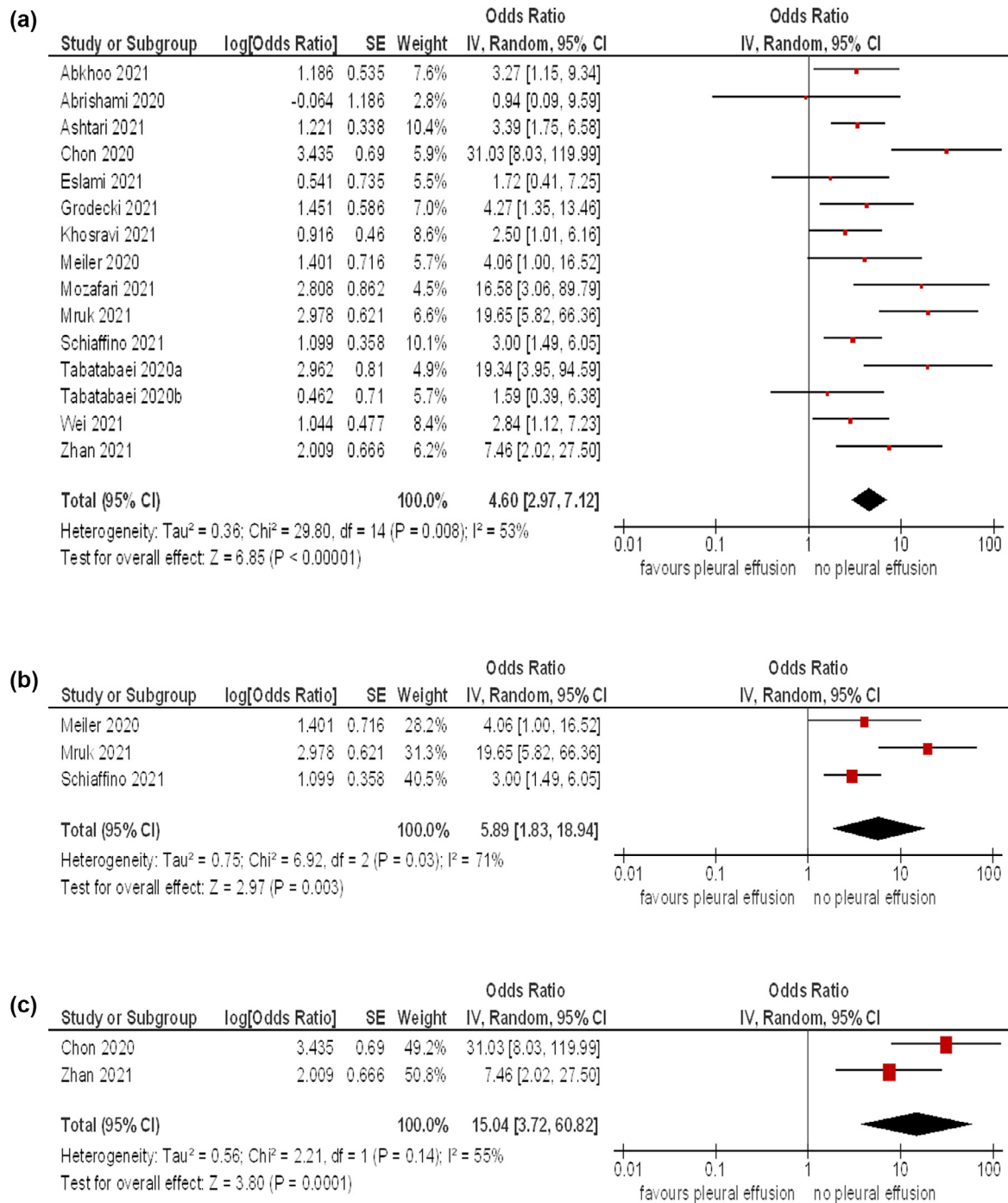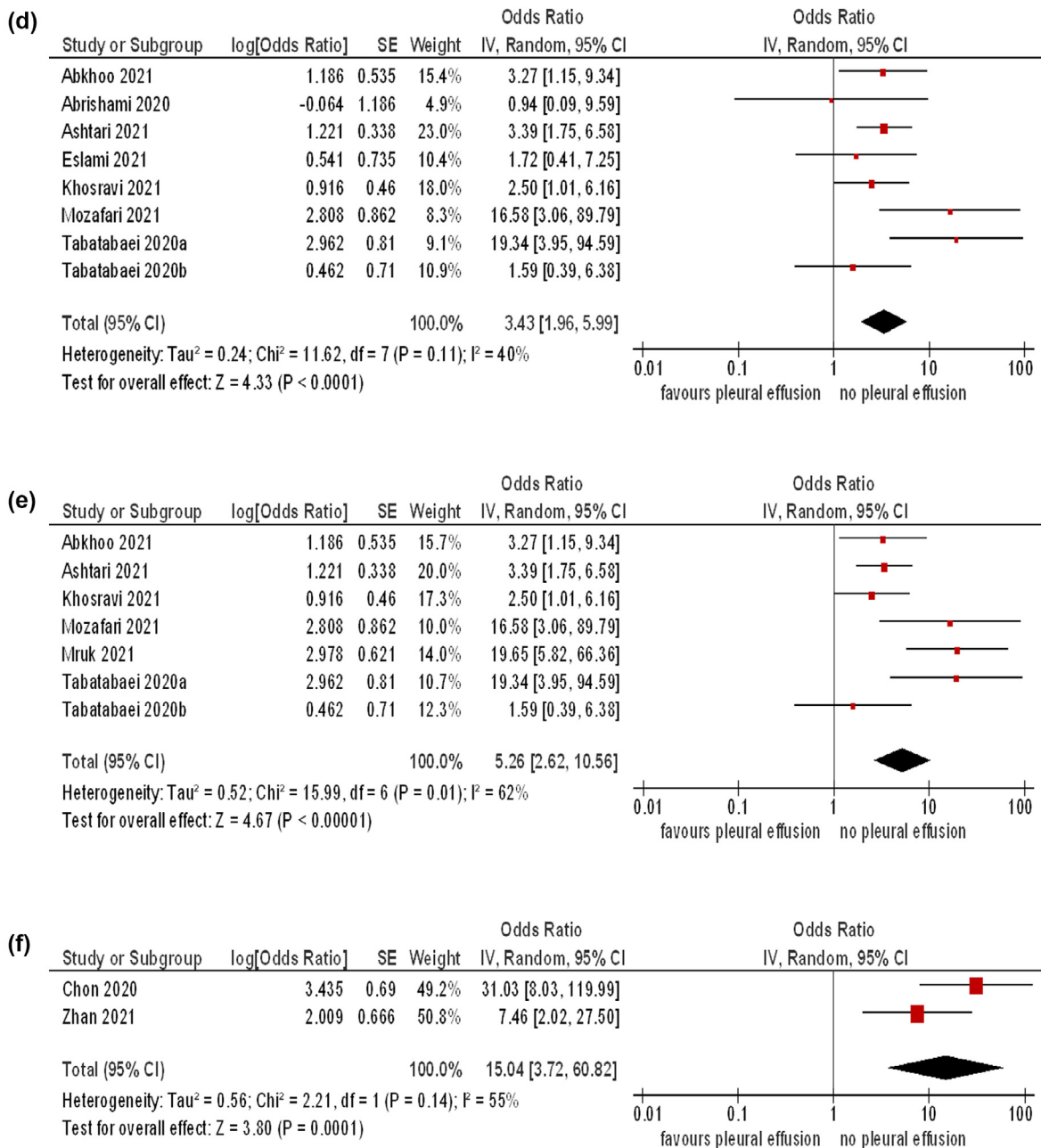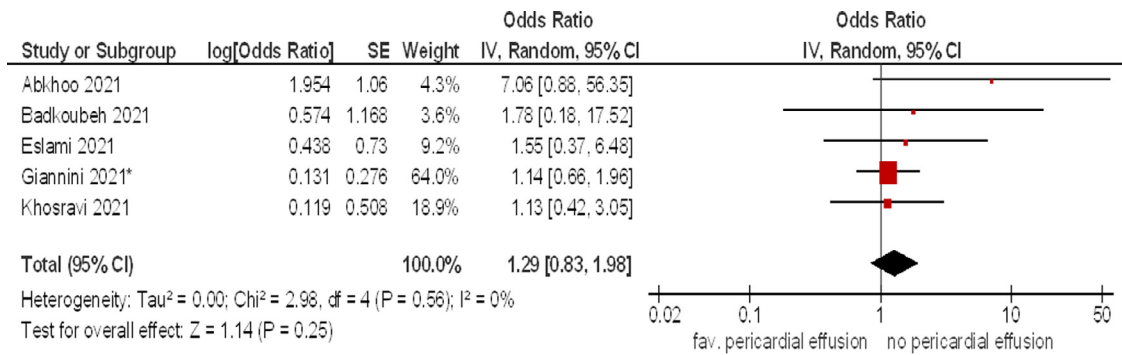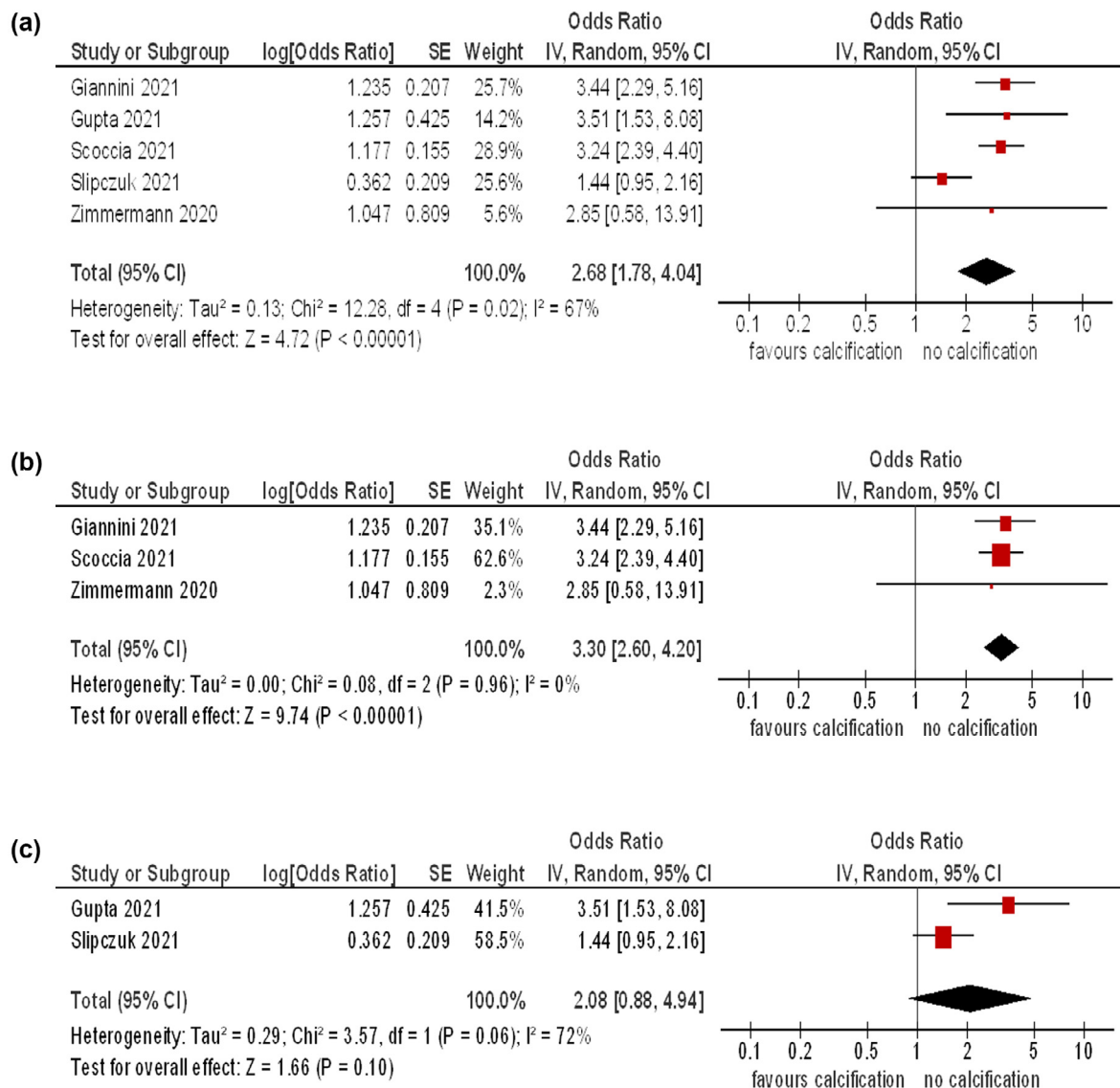

Figure 5. (a) Forrest plots of the odds ratios for the effect of coronary calcification on in-hospital mortality in COVID-19. The pooled odds ratio was 2.68 (95% CI 1.78-4.04). (b) The pooled odds ratio for coronary calcification in the included investigations from Europe was 3.30 (95% CI 2.60-4.20). (c) The pooled odds ratio for coronary calcification in the included studies from the USA was 2.08 (95% CI 0.88-4.94). (Color version of figure is available online.)
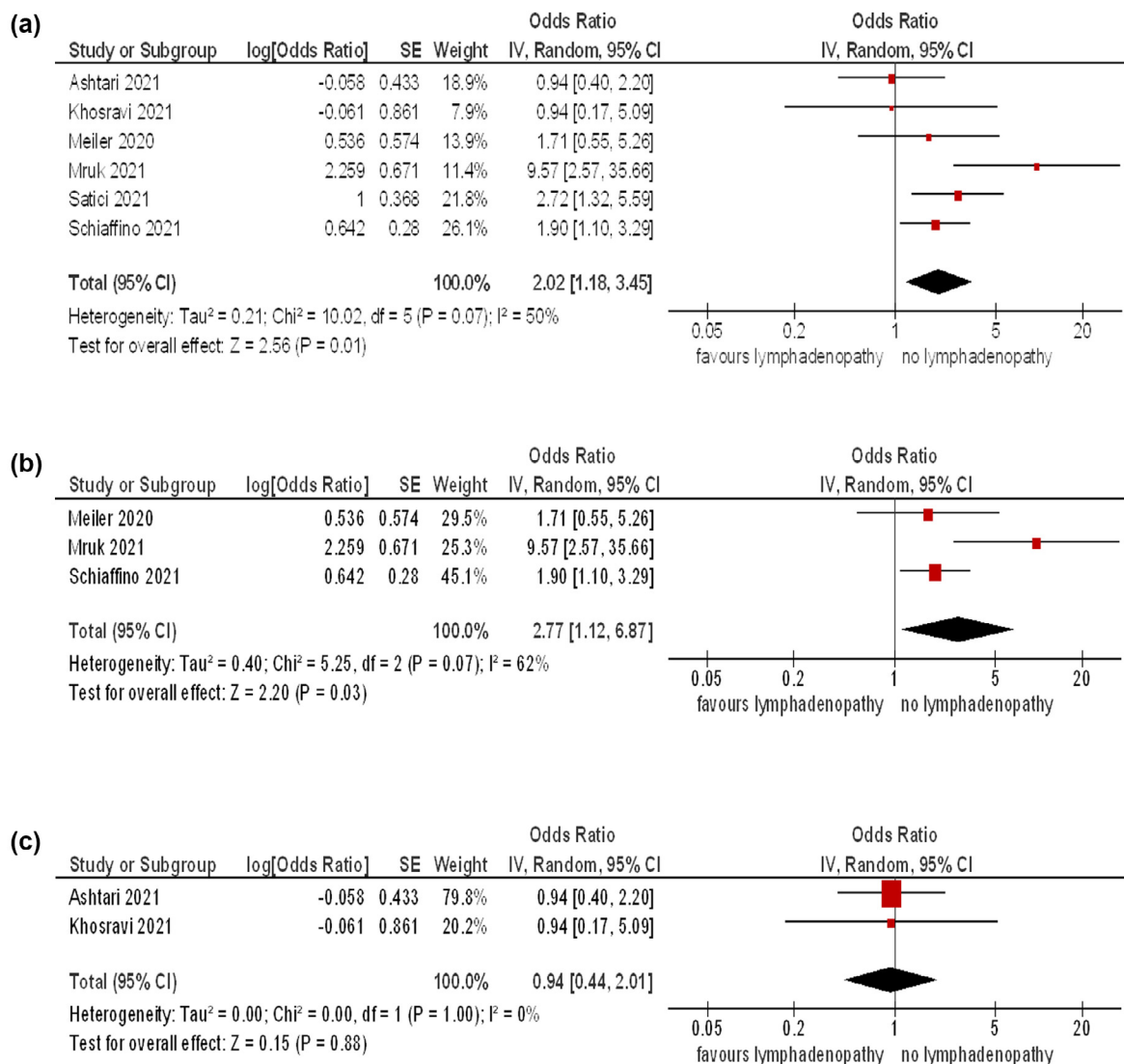
Figure 6. (a) Forrest plots of the odds ratios for the effect of mediastinal lymphadenopathy on in-hospital mortality in COVID-19. The pooled odds ratio was 2.02 (95% CI 1.18-3.45). (b) The pooled odds ratio for mediastinal lymphadenopathy based on the acquired studies from Europe was 2.77 (95% CI 1.12-6.87). (c) The pooled odds ratio for mediastinal lymphadenopathy based on the collected reports from Iran was 0.94 (95% CI 0.44-2.01). (Color version of figure is available online.)

present analysis. However, in most studies. CTs were performed at hospital admission.

Risk stratification of COVID-19 patients is very crucial for treatment planning. Important clinical parameters were identified, and several scores were proposed to predict mortality in COVID-19 (40). A recent study could show that a score based on serological parameters comprising white blood cells, C-reactive protein, lymphocyte $\geq 0.8 \times 10^9$/L, and lactate dehydrogenase ≥ 400 U/L was highly accurate to predict survival with an area under the curve of 0.95 (40).

Very early on during the pandemic, it was shown that cardiovascular co-morbidities, especially coronary heart disease are an important risk factor for a severe COVID-19 course (43). The present analysis can agree with this with a significant association between coronary calcification on CT images as an imaging finding of coronary heart disease. Clearly, there are

cases of patients with amnestic known coronary heart disease without calcified plaques, which are not covered by this approach. Secondly, thoracic CT without contrast media application, and electrocardiogram triggering cannot be considered as a diagnostic gold standard for cardiac imaging. However, the sole presence of calcified plaques in CT performed for COVID-19 evaluation can be suspicious for an unfavorable outcome. Moreover, promising data indicated that quantification of coronary plaques using scores is even better to predict unfavorable outcomes (19,29). As a shortcoming of the present study, we could not pool the results of these plaque scores further due to differences in the included studies. To harmonize the data, we only include the dichotomized analyses of presence of coronary plaque or not.

Pleural effusion was the strongest predictor for mortality in the presented results. It was early on discussed as a rare finding

in patients with COVID-19 (44) and was stated to be more characteristic for other disorders, as pleural effusion is very common in critical ill patients. Clearly, there are many causes of pleural effusion, including viral pleuritis, congestive heart failure or cancer (33).

As early on stated, extrapulmonary imaging findings may indicate the occurrence of severe inflammation as identified by Li and colleagues (9). Another explanation was given that pleural effusion might indicate a bacterial superinfection as a severe complication of the COVID-19 infection.

In a comprehensive meta-analysis of prognostic factors in COVID-19, pleural effusion showed even a higher odds ratio for severe course, and mortality than pulmonary consolidation (OR of 3.31 versus 2.46) (45). However, this analysis only included studies up to April 2020, which could explain the different results to the present study.

Unfortunately, most studies did not report the size of the pleural effusion. It is yet unknown, whether the size has also a significant effect on mortality of COVID-19 patients.

Mediastinal lymphadenopathy is also an imaging finding, which was considered as rare in COVID-19 (7). It was also discussed as a possible sign for bacterial superinfection. The frequency of mediastinal lymphadenopathy was reported to be up to 29% (26). Of note, the frequency can differ according to the threshold value of enlargement. All included studies used 10 mm in short axis. In a recent study investigating 650 patients employed the threshold value of 10 mm, the frequency of mediastinal lymphadenopathy was 8.6% (26). The identified odds ratio for 30-days mortality in this mentioned study was 2.38 (95% 1.13-4.98) (26).

The only investigated CT finding not associated with mortality was pericardial effusion. In a small study based on 54 patients, a significant difference was identified between a severe and a critical patient group in regard of pericardial effusions ($n = 1$, 2.6%, $n = 5$, 33.3%, $p < 0.01$) (46). The presumed reason for the pericardial effusion was inflammatory effusion (46). Contrary to the present results, the authors used echocardiography, which might be more sensitive for detection of pericardial effusion in comparison to CT. According to Wang et al., cardiac injury caused by COVID-19 infection may also provoke pericardial effusion (3).

However, the present data can lead to the assumption that pericardial effusion is not a significant predictor for mortality.

Notably, the investigated studies included only patients of the first wave of the pandemic, which has a relevant impact on the results (47), as the mortality rates are declining since then. Due to less experience in care of COVID-19 patients and less knowledge of the disease in general, the course of COVID-19 patients might be worse than in recent days of the pandemic. Moreover, the possible effect of the current vaccination campaigns on COVID-19 mortality cannot be addressed by the present analysis.

The present analysis could show substantial differences between different origins of the investigated studies. This could explain the heterogeneity in this meta-analysis.

Interestingly, for pleural effusion, the pooled odds ratio was higher for studies from China compared to those in the studies performed in USA, Europe, and Iran. Furthermore, for coronary calcifications, no relevant difference between the studies from USA, and Europe were identified. Finally, for mediastinal lymphadenopathy, however, the pooled odds ratio was low in the sub-analysis for studies from Iran, whereas in the sub-analysis for studies from Europe, it was high. These findings are difficult to explain. Presumably, different virus subtypes may play a role. Another explanation may be the different beginning of the pandemic throughout the countries. China was the origin of COVID-19 and had less experience with this disease compared to the other world regions. There were also differences according to gender ratios and mean ages of the investigated patients.

The present meta-analysis has several limitations to address. First, it is comprised of published studies with between studies mainly caused by slightly different patient samples, and different study designs. Different countries with resulting different strategies for COVID-19 treatment and health care capabilities might also result in inhomogeneities. Second, there is the restriction to English language. Third, the presented results only rely on patient samples of the first wave of the pandemic. The results cannot be considered representative for the current state of the pandemic. Fourth, different CT scanner technology was used in the studies, ranging from 16 slices to 256 slices. There might be only small diagnostic accuracy differences between the different scanners used. One can consider the investigated CT findings of the present study as very stable to be accurately diagnosed on all CT scanners employed in clinical routine. Fourth, the included studies are restricted to COVID-19 patients, which were investigated by initial CT. This results in potential selection bias as most patients with COVID-19 are not diagnosed by CT. Forth, the exact timepoint of the CT was not clearly stated in 27.3% of studies. This could result in certain bias, when CT imaging was not performed at admission of the patients. However, in most studies CT was performed as a base line imaging directly at the admission of the hospital.

In conclusion, pleural effusion, coronary calcification, and mediastinal lymphadenopathy are associated with in-hospital mortality in COVID-19 patients. These extrapulmonary findings should be sufficiently reported by the radiologist and should be considered as highly clinically relevant.

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None.

AVAILABILITY OF SUPPORTING DATA

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of Interest

We declare no competing interests.

Data Sharing Statement

The data can be provided upon reasonable request by the corresponding author.

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