Thieme

Prevalence and prognostic role of thoracic lymphadenopathy in Covid-19

Prävalenz und prognostische Rolle der thorakalen Lymphadenopathie bei Covid-19

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ABSTRACT

Purpose The prevalent coronavirus disease 2019 (COVID-19) pandemic has spread throughout the world and is considered a serious threat to global health. The prognostic role of thoracic lymphadenopathy in COVID-19 is unclear. The aim of the present meta-analysis was to analyze the prognostic role of thoracic lymphadenopathy for the prediction of 30-day mortality in patients with COVID-19.

Materials and Methods The MEDLINE library, Cochrane, and SCOPUS databases were screened for associations between

CT-defined features and mortality in COVID-19 patients up to June 2021. In total, 21 studies were included in the present analysis. The quality of the included studies was assessed by the Newcastle-Ottawa Scale. The meta-analysis was performed using RevMan 5.3. Heterogeneity was calculated by means of the inconsistency index I2. DerSimonian and Laird random-effect models with inverse variance weights were performed without any further correction.

Results The included studies comprised 4621 patients. The prevalence of thoracic lymphadenopathy varied between 1 % and 73.4 %. The pooled prevalence was 16.7 %, 95 % CI = (15.6 %; 17.8 %). The hospital mortality was higher in patients with thoracic lymphadenopathy (34.7 %) than in patients without (20.0 %). The pooled odds ratio for the influence of thoracic lymphadenopathy on mortality was 2.13 (95 % CI = [1.80–2.52], p < 0.001).

Conclusion The prevalence of thoracic lymphadenopathy in COVID-19 is 16.7 %. The presence of thoracic lymphadenopathy is associated with an approximately twofold increase in the risk for hospital mortality in COVID-19.

Key Points

- The prevalence of lymphadenopathy in COVID-19 is 16.7 %.
- Patients with lymphadenopathy in COVID-19 have a higher risk of mortality during hospitalization.
- Lymphadenopathy nearly doubles mortality and plays an important prognostic role.

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ZUSAMMENFASSUNG

Ziel Die Coronavirus-Pandemie 2019 (COVID-19) hat sich weltweit ausgebreitet und stellt nach wie vor eine ernste Bedrohung für die globale Gesundheit dar. Die prognostische Rolle der thorakalen Lymphadenopathie bei Covid-19 ist unklar. Ziel der vorliegenden systematischen Übersichtsarbeit und Meta-Analyse war es, die prognostische Rolle der thorakalen Lymphadenopathie für die Vorhersage der hospitalen Mortalität bei Patienten mit COVID-19 zu analysieren.

Materialien und Methoden Die Datenbanken MEDLINE, Cochrane und SCOPUS wurden nach thorakaler Lymphadenopathie und der intrahospitalen Mortalität bei COVID-19-Patienten bis Juni 2023 durchsucht. Insgesamt waren 21 Studien für die Analyse geeignet und wurden in die vorliegende Studie aufgenommen. Die Qualität der eingeschlossenen Studien wurde anhand der Newcastle-Ottawa-Skala eingeschätzt. Die Meta-Analyse wurde mit RevMan 5.3 durchgeführt. Die Heterogenität wurde mit dem Inkonsistenzindex (I^2) berechnet. Der Simonian und Laird Random-Effects-Modelle mit inversen Varianzgewichtungen wurden ohne weitere Korrekturen durchgeführt.

Ergebnisse Die eingeschlossenen Studien umfassten 4621 Patienten. Die Prävalenz der mediastinalen Lymphadenopathie variierte in den Studien zwischen 1 % und 73,4 %. Die gepoolte Prävalenz betrug 16,7 % mit 95 % CI = (15,6 %; 17,8 %). Die hospitale Mortalität war bei Patienten mit mediastinaler Lymphadenopathie höher (34,7 %) als bei Patienten ohne mediastinale Lymphadenopathie (20,0 %). Die gepoolte Odds Ratio für den Einfluss der mediastinalen Lymphadenopathie auf die Mortalität betrug 2,13 (95 % CI = [1,80–2,52]; p < 0,001).

Schlussfolgerung Thorakale Lymphadenopathie tritt in 16,7 % bei Patienten mit COVID-19 auf. Bei COVID-19 ist das Vorhandensein einer thorakalen Lymphadenopathie mit einem etwa zweifach erhöhten Risiko der Krankenhausmortalität verbunden.

Kernaussagen

- Die Prävalenz der COVID-19-Lymphadenopathie beträgt 16,7 %.
- Patienten mit COVID-19-Lymphadenopathie haben ein erhöhtes Krankenhausmortalitätsrisiko.
- Bei Lymphadenopathie besteht eine nahezu verdoppelte Mortalitätsrate.

Introduction

The WHO declared COVID-19a pandemic in March 2020, only a few months after the first infections were detected in December 2019. Since then, the management of COVID-19 has presented previously unimagined challenges for global health care systems.

The spectrum of disease presentation varies from largely asymptomatic to fulminant disease resulting in death [1–5]. Reliable prediction of severe disease courses can guide resource planning particularly during times of peak demand and also has the potential to control treatment measures. The identification of risk factors for a severe disease course is thus still of decisive importance for the clinical care of patients [2]. The already established prognostic factors include an age of more than 60 years and male sex [6–8]. Comorbidities like cardiac insufficiency, vascular diseases, and dementia are also predictors for a severe disease course [6].

Computed tomography (CT) is the diagnostic imaging method of choice in patients with COVID-19 and is used clinically to detect lung consolidations and to rule out complications [2, 9–11]. Moreover, extrapulmonary findings like pleural effusion, pericardial effusion, mediastinal lymphadenopathy, and coronary calcifications can be diagnosed via CT and provide prognostically useful information [11]. CT also shows numerous secondary findings some of which are directly associated with the disease (e. g., pleural effusion, pericardial effusion, mediastinal lymphadenopathy) [9], while others are patient-specific (e. g., coronary calcification) [12, 13]. However, the available studies on the predictive relevance of these findings are heterogeneous. The presence of a pleural effusion, for example, was identified as a prognostically

relevant risk factor [13]. The prognostic significance of thoracic lymphadenopathy is still unclear. Some studies show a connection between lymphadenopathy and a severe disease course. However, most published studies on this topic include only a small number of patients. The goal of this study is therefore to analyze the prognostic importance of thoracic lymphadenopathy for the prediction of in-hospital mortality in patients with COVID-19 based on a systematic meta-analysis.

Methods

Data collection

Since this study was performed as a meta-analysis with systematic analysis, ethics review was not required. The MEDLINE, Cochrane, and SCOPUS databases were searched for thoracic lymphadenopathy and in-hospital mortality in COVID-19 patients from the beginning of January 2020 to the end of June 2023. The studies were selected in relation to the prognostic value of mediastinal lymphadenopathy.

The primary end point of the systematic review was the odds ratio of CT findings regarding in-hospital mortality.

The following search terms were used for the database search: "COVID-19" AND "computed tomography" OR "CT" AND "mortality" OR "severe course" OR "death". The identification and the subsequent selection of the studies to be included were performed on the basis of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [14]. The selection process is shown in the PRISMA flowchart (▶ **Fig. 1**).

The inclusion criteria for the studies (or subgroups of studies) were:

(1) COVID-19 diagnosis based on reverse transcriptase-polymerase chain reaction (RT-PCR), (2) provision of CT findings, (3) provision of odds ratio or hazard ratio with confidence interval (CI).

The exclusion criteria were: (1) Systematic reviews, (2) case reports, (3) not written in the English language, (4) imaging methods other than CT.

Data extraction

Data was recorded by one author (JO) and checked for correctness in connection with an independent instance (AS). For every study, details regarding the study design, publication year, country of origin, number of patients, patient characteristics (age and sex), diagnosis, treatment, CT finding, time point of CT examination, survival data, and adjustment factors were recorded.

Quality analysis

The quality of the included studies was evaluated on the basis of the Newcastle-Ottawa Scale (NOS) [15]. The evaluation of the study quality was performed by two authors (HJM, AS) and included mainly the selection of cases, the comparability of the cohorts, and the outcome assessment of risk exposure. Every study was assigned a score of 0–9, with a study with a score ≥ 6 being classified as high quality [15].

Statistical analysis

The meta-analysis was performed using RevMan 5.3 (2014; Cochrane Collaboration, Copenhagen, Denmark). The heterogeneity was calculated with the inconsistency index (I^2) [16, 17]. The DerSimonian and the Random Effects model with inverse variance weighting was applied without further correction [18]. The publication bias was reviewed with a funnel plot and the Egger's test [19].

Results

Quality of included studies

In total, 21 studies were included in the analysis [20–40].

Only 1 of the 21 included studies is prospective (4.8 %). The rest are retrospective (▶ **Table 1**). As the high NOS values of the studies (5–8 points) show, the risk of a systematic bias can be considered low (▶ **Table 2**). Two studies do not specify the exact duration of patient recruiting which could result in a possible bias. In multiple studies the exact time point of CT was not sufficiently specified which could also result in a bias.

The funnel chart in ▶ **Fig. 2** does not indicate a publication bias. The Egger's test did not show any statistically significant asymmetry (P = 0.58).

Patients

The included studies involve 4621 patients. There were 1785 women (38.6 %) and 2836 men (61.4 %) with an average age of 60.1 years. In all studies COVID-19 was diagnosed with RT-PCR.

Most studies were performed between February and April 2020 and are shown in ▶ **Table 1**. Two studies did not specify the exact time period.

12 studies were performed in the Near East and Middle East, corresponding to 54 % of all studies. 5 studies were performed in Europe (22 %), 3 in Asia (14 %), 1 in Africa (5 %), and 1 in North America (5 %).

Mediastinal lymphadenopathy

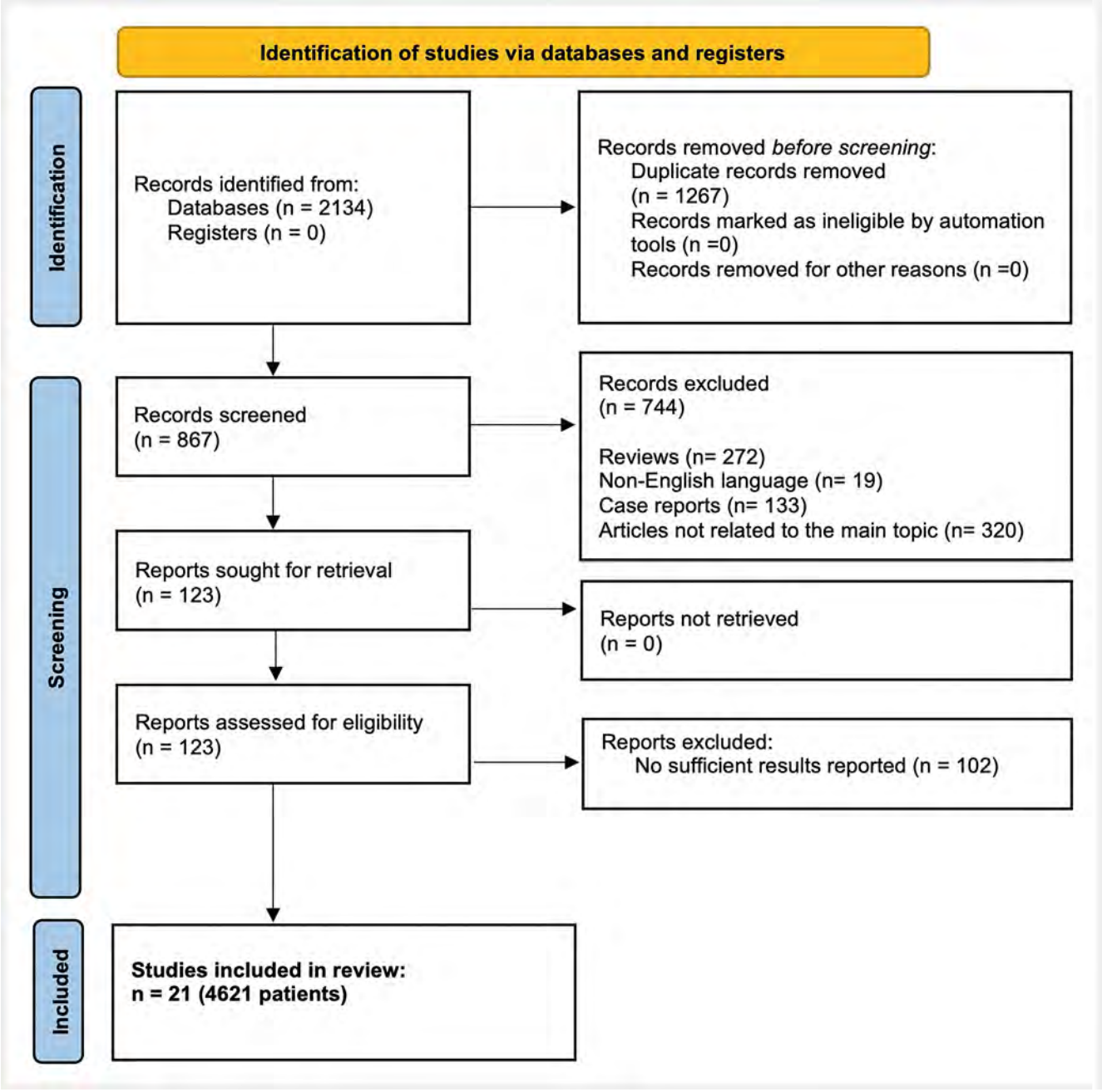
The prevalence of mediastinal lymphadenopathy varied in the studies between 1 % and 73.4 %. The pooled prevalence was 16.7 % with 95 % CI (15.6 %; 17.8 %).

In-hospital mortality was higher in patients with mediastinal lymphadenopathy (34.7 %) than in patients without mediastinal lymphadenopathy (20.0 %). The pooled odds ratio for the relationship between mediastinal lymphadenopathy and mortality was 2.13 (95 % CI = [1.80; 2.52]; p < 0.001).

Discussion

The present meta-analysis was able to show a significant effect of thoracic lymphadenopathy on in-hospital mortality in patients with COVID-19.

The identification of reliable prognostic parameters is important since COVID-19 has a high mortality rate in patients with a severe course, with the mortality rate being up to 20 % in pa-



▶ **Fig. 1** PRISMA flowchart of paper acquisition.

tients admitted to the intensive care unit (ICU) [2–6]. Already established prognostic parameters are an age of over 60 years and male sex as well as a shorter time period between the start of symptoms and admittance to the emergency room as an indicator of rapid disease dynamics [1, 3, 6, 8]. Moreover, the extent of pulmonary consolidation on CT images is also prognostically relevant [2, 41, 42]. These consolidations are an indication of disease progression and are most pronounced around the tenth day of illness [12].

Thoracic lymphadenopathy is an imaging finding that was not considered to have central importance at the beginning of the COVID-19 pandemic [9]. It was also discussed as a diagnostic indication of a bacterial superinfection. In the beginning, the rate of mediastinal lymphadenopathy was only 3.4 % [42]. In a meta-analysis, the rate ranged from 5 % to 28 % [13]. It must be taken into consideration that the rate can differ depending on the enlargement threshold value. A common threshold value was 10 mm in the short axis in most studies [13].

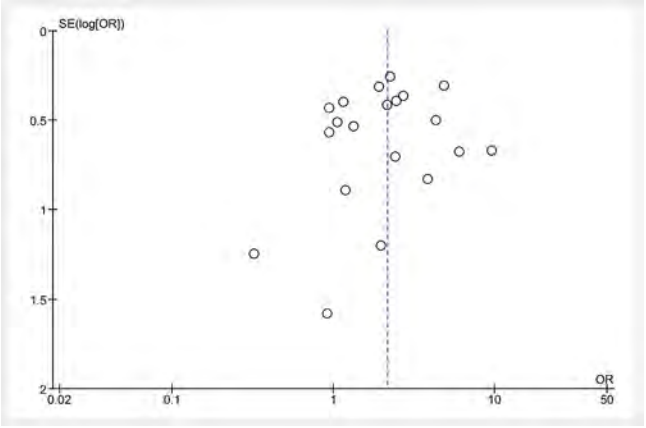
Risk stratification of COVID-19 patients is essential for treatment planning. Therefore, prognostically decisive clinical parameters were determined and multiple scores for predicting mortality in COVID-19 were proposed [43]. As an example, serological parameters, including white blood cells, C-reactive protein, lymphocytes ≥ 0.8 × 10^9/L, and lactate dehydrogenase ≥ 400 U/L,

▶ **Table 1** Included studies and patients.

Author	Study design	Country	Year	Time period	Number of patients	Number of patients who survived	Number of patients who died	Patients with lymphadenopathy	Lymphadenopathy in surviving patients	Lymphadenopathy in patients who died
Abbasi et al. [15]	Retrospective	Iran	2021	02/2020–03/2020	262	206	56	6	3	3
Abrishami et al. [16]	Retrospective	Iran	2020	Unclear	43	38	5	3	3	0
Ashtari et al. [17]	Retrospective	Iran	2021	02/2020–03/2020	363	259	104	29	21	8
Collado-Chagoya et al. [18]	Retrospective	Mexico	2022	04/2020–06/2020	124	101	23	27	21	6
Colombi et al. [19]	Retrospective	Italy	2020	02/2020–03/2020	248	170	78	56	32	24
Eslami et al. [20]	Prospective	Iran	2021	02/2020–04/2020	87	74	13	4	3	1
Gunduz et al. [21]	Retrospective	Turkey	2022	03/2020–09/2020	198	122	76	13	3	10
Li et al. [22]	Retrospective	China	2021	01/2020–04/2020	147	123	24	24	15	9
Kavosi et al. [23]	Unclear	Iran	2022	10/2020–12/2020	389	275	114	31	21	10
Kaya et al. [24]	Retrospective	Turkey	2022	01/2021–05/2021	250	173	77	125	67	58
Khosravi et al. [25]	Retrospective	Iran	2020	02/2020–04/2020	121	85	36	6	4	2
Lee et al. [26]	Retrospective	Korea	2022	02/2020–03/2020	344	334	10	53	50	3
Meyer et al. [27]	Retrospective	Germany	2023	03/2020–06/2022	177	124	53	130	86	44
Mruk et al. [28]	Retrospective	Poland	2021	Unclear	156	141	15	15	10	5
Pilechian et al. [29]	Retrospective	Iran	2021	04/2020–08/2020	195	147	48	35	21	14
Qayyum et al. [30]	Prospective	Pakistan	2022	06/2020–07/2020	155	130	25	36	30	6
Sampsonas et al. [31]	Retrospective	Greece	2022	02/2021–06/2021	53	26	27	33	17	16
Sardanelli et al. [32]	Retrospective	Italy	2020	02/2020–03/2020	410	274	136	76	39	37
Satici et al. [33]	Retrospective	Turkey	2021	04/2020–05/2020	650	594	56	60	49	11
Tharwat et al. [34]	Retrospective	Egypt	2022	06/2020–05/2021	100	40	60	3	2	1
Yang et al. [35]	Retrospective	China	2020	01/2020–02/2020	149	149	0	7	7	0

▶ **Table 2** Quality of included studies based on the NOS scale. A positive evaluation of the study features is indicated by an "X".

Study	Adequate definition of the patients	Representation of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the study design	Study inclusion	Use of the same methods for cases and controls
Abbasi et al. 2021	x	x	x	x	x	x	x
Abrishami et al. 2010			x	x	x	x	x
Ashtari et al. 2021	x	x	x	x	x	x	x
Collado-Chagoya et al. 2022	x	x	x	x	x	x	x
Colombi et al. 2020	x	x	x	x	x	x	x
Eslami et al. 2021	x	x	x	x	x	x	x
Gunduz et al. 2022	x	x	x	x	x	x	x
Kavosi et al. 2022	x	x	x	x	x	x	x
Kaya et al. 2022	x	x	x	x	x	x	x
Khosravi et al. 2020	x	x	x	x	x	x	x
Lee et al. 2022	x	x	x	x	x	x	x
Hailan Li et al. 2021	x	x	x	x	x	x	x
Pilechian et al. 2021	x	x	x	x	x	x	x
Qayyum et al. 2022	x	x	x	x	x	x	x
Sampsonas et al. 2022	x	x	x	x	x		x
Sardanelli et al. 2020	x	x	x	x	x	x	x
Satici et al. 2021	x	x	x	x	x	x	x
Tharwat et al. 2022	x	x	x	x	x	x	x
Yang et al. 2020	x	x	x	x	x		x
Meyer et al. 2023	x	x	x	x	x	x	x
Mruk et al. 2021			x	x	x	x	x



▶ **Fig. 2** Funnel chart of acquired publications to show publication bias.

were used in one study to calculate a score. This score was capable of predicting survival very precisely with an AUC of 0.95 [44].

The introduction of the vaccine changed the course of the pandemic. However, there are still fatal COVID-19 courses and correct diagnosis and treatment are still highly relevant – particularly in countries with a poor health care system and a low vaccination rate [24–26].

Time dependence was examined in a recently conducted meta-analysis of CT findings in COVID-19 patients [45]. Thoracic lymphadenopathy was detected more frequently in later disease stages than in the early stage (15 % vs. 5 %) [45]. A more recent study was able to show that mediastinal lymphadenopathy is a factor indicating COVID-19 pneumonia compared to non-COVID pneumonia [46]. Sampsonas et al. also showed that mediastinal lymphadenopathy is significantly associated with lung involvement but not with mortality [36].

Qayyum et al. examined 150 patients with acute COVID-19 infection and found prevalent mediastinal lymphadenopathy with a frequency of 23.2 % [34]. Moreover, they did not observe any connection between lymphadenopathy and mortality [35]. Erturk et al. detected lymphadenopathy in over 52 % of patients that correlated significantly with the duration of hospital stay [47].

In another recently published study including 344 patients, the prevalence of lymphadenopathy was 15.4 % and was associated with a higher risk of admittance to the intensive care unit (odds ratio: 3.25; 95 % confidence interval 1.06–9.95) but not with a significant risk for in-hospital mortality [30].

Histopathology showed that the affected lymph nodes had significant capillary congestion and edema, an increase in extrafollicular plasmablasts, mild to moderate plasmacytosis, a dominant population of CD8 + T-cells, and histiocytosis with hemophagocytic activity as a morphological correlate [48]. The significance of the prognostic relevance of lymphadenopathy could be explained by the impairment of the immune system by the disease.

Multiple limitations must be taken into consideration in the present meta-analysis. The analyzed studies are retrospective studies with comparably small cohorts. There could be a selection bias that could affect the results. Moreover, the rate of fatal cases is high due to the inclusion of patients in the first wave of the pandemic in the analysis. Therefore, the present results may not be representative for patient samples with a lower mortality rate.

Conclusion: Thoracic lymphadenopathy occurs in approximately 17 % of all patients with COVID-19. The presence of thoracic lymphadenopathy indicates an approximately two-fold increase in the risk for in-hospital mortality.

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Conflict of Interest

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