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Clinical importance of thoracal lymphadenopathy in COVID-19

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ABSTRACT

Background: Thoracal lymphadenopathy may predict prognosis in patients with coronavirus disease 2019 (COVID-19), albeit the reported data is inconclusive. The aim of the present analysis was to analyze the affected lymph node stations and the cumulative lymph node size derived from computed tomography (CT) for prediction of 30-day mortality in patients with COVID-19.

Methods: The clinical database was retrospectively screened for patients with COVID-19 between 2020 and 2022. Overall, 177 patients (63 female, 35.6%) were included into the analysis. Thoracal lymphadenopathy was defined by short axis diameter above 10 mm. Cumulative lymph node size of the largest lymph nodes was calculated and the amount of affected lymph node stations was quantified.

Results: Overall, 53 patients (29.9%) died within the 30-day observation period. 108 patients (61.0%) were admitted to the ICU and 91 patients needed to be intubated (51.4%). Overall, there were 130 patients with lymphadenopathy (73.4%). The mean number of affected lymph node levels were higher in non-survivors compared to survivors (mean, 4.0 vs 2.2, $p < 0.001$). The cumulative size was also higher in non-survivors compared to survivors (mean 55.9 mm versus 44.1 mm, $p = 0.006$). Presence of lymphadenopathy was associated with 30-day mortality in a multivariable analysis, OR = 2.99 (95% CI 1.20 – 7.43), $p = 0.02$.

Conclusions: Thoracal lymphadenopathy comprising cumulative size and affected levels derived from CT images is associated with 30-day mortality in patients with COVID-19. COVID-19 patients presenting with thoracic lymphadenopathy should be considered as a risk group.

Introduction

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

The clinical course of COVID-19 can be highly variable with patients with no symptoms or rapid deterioration to a critical illness and potentially fatal outcome [1–5].

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 is crucial for clinical patient care to this day [2].

Already established clinical prognostic factors are age over 60 years and male sex [6–8]. Comorbidities like dementia, heart failure and peripheral vascular diseases are also predictors of an unfavourable course [6].

Computed tomography (CT) is the diagnostic imaging modality of choice in patients with COVID-19. It is clinically used for detection of pulmonary consolidations and to rule out differential diagnosis [2,9–11]. Notably, extrapulmonary findings, such as pleural effusion, pericardial effusion, mediastinal lymphadenopathy, and coronary calcifications can be diagnosed by CT and harbor prognostic information [11].

The extrapulmonary findings were initially described as atypical and should raise the concerns for possible differential diagnoses [9]. However, even early published data raised concerns that these findings might predict a more severe or lethal course of the disease [12,13].

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So far, the presence of mediastinal lymphadenopathy was identified as a relevant prognostic risk factor with a reported odds ratio of 2.02 (95% CI 1.18–3.45) for unfavorable outcome in a recent meta analysis [14]. However, the reported studies are heterogeneous with different cut-off values for lymph node size. Moreover, there was no analysis regarding the affected lymph node levels or a reported cumulative lymph node size. Beyond that, it should be emphasized that most studies provide data regarding the first wave of the pandemic [14], which differs strongly from the present status of the pandemic due to the advent of different subtypes of the virus and the development of the vaccination [15–17].

Therefore, there is need to provide a quantitative analysis of thoracal lymph nodes including size and the number of affected lymph node stations.

The purpose of the present study was to investigate the prognostic role of thoracal lymph nodes on 30-day mortality in patients with COVID-19.

Materials and methods

Patient acquisition

The present retrospective study was approved by the institutional review board (University of Magdeburg, nr. 25/21).

All patients with COVID-19 were retrospectively assessed within the time period 2020–2022. Inclusion criteria for the study were:

1. available thoracal CT images at the time of admission of the hospital.

1. available clinical data including survival within the 30-day period, need for intubation and need for ICU admission.
2. RT-PCR-proven COVID-19 infection.
3. previous COVID-19 vaccination at least one month or more prior to the hospital admission.

Exclusion criteria were:

1. severe image artifacts (i.e., due to implants or motion artifacts) as well as any form of previous treatment.
2. missing clinical data/follow up.

Clinical parameters

The following clinical parameters were retrieved of the patient records at the time point of admission. Age, gender, admission to intensive care unit (ICU), duration of mechanical ventilation in hours, 30-day mortality.

Imaging technique

CT was performed at admission to the hospital for every patient without any previous treatment. All CT scans were obtained on a multidetector CT scanner (Siemens Somatom Definition AS+; Siemens Healthcare, Germany). During the first year of the COVID-19 pandemic the scanner was set aside for suspected or confirmed cases of COVID-19. Patients were positioned in supine position. The CT protocol was as follows: Acquisition slice thickness 1 mm with 5 mm reconstructions, tube voltage 120 kV, automatic tube current modulation, pitch factor 1.2, and collimation 0.6 mm. In all cases contrast media was given. Fig. 1 displays a representative case of the patient sample for illustration purposes.

Thoracal lymph node

All thoracal lymph nodes were investigated of each patient. A cut-off value of 10 mm for the short axis was used to determine pathological enlargement. The American Thoracic Society lymph node map was used to evaluate the involved lymph node levels [18,19]. In total, 14 stations are reported divided by supraclavicular station 1, upper zone station 2–4, aortopulmonary zone 5 and 6, subcarinal zone station 7, lower zone station 8 and 9, and hilar zone 10–14 [18,19].

For this study, the presence of lymphadenopathy was notified. Lymphadenopathy was determined if one of the analysed lymph nodes was enlarged with a cut-off value. Finally, the cumulative size of the lymph nodes was calculated as a sum of all short axis diameters of the largest lymph nodes per level. The amount of affected lymph node stations was quantified.

Pulmonary score

A reliable and established visual score was used for the analysis of pulmonary consolidation [20]. In short, each of the 5 lung lobes were visually assessed to determine the presence of ground glass opacities or consolidation and degree of extension. Each lobe extent was classified as having a score from 0 to 4, when none, minimal (1–25%), mild (26–50%), moderate (51–75%), or severe (> 75%) extension was visually estimated, respectively. The number of lung lobes involved per patient by GGO or consolidation opacities was also estimated as a first visual CT score to assess the extent of lung damage. Finally, by summing the visual scores of the 5 lobes, the score was evaluated over a range from 0 to 20.

Statistical analysis

The statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, version 225.0: IBM corporation). Graphics creation was performed using GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA). Collected data were evaluated by means of descriptive statistics (absolute and relative frequencies). Spearman's correlation coefficient (r) was used to analyze associations between investigated scores after testing for normality distribution. Group differences were calculated with Mann-Whitney test and Fisher exact test, when suitable. Uni-and multivariable regression analysis was employed to investigate the associations with 30-day mortality. In all instances, p-values < 0.05 were taken to indicate statistical significance.

Results

Overall, 177 patients (63 female, 35.6%) were included into the present analysis. The mean age at the time of CT-acquisition was 64.0 ± 15.3 years, median age 65 years.

Clinical data and thoracal lymphadenopathy

Overall, 53 patients (29.9%) died within the 30-day observation period. 108 patients (61.0%) were admitted to the ICU and 91 patients were intubated (51.4%). Lymphadenopathy was identified in 130 patients (73.4%).

In the survivor group, there were 86 patients (69.9%) with lymphadenopathy, whereas in non-survivor group there were 44 patients (84.6%) with lymphadenopathy, p = 0.06. The mean number of affected lymph node levels were higher in non-survivors compared to the survivors (mean, 4.0 vs 2.2, p < 0.001). The cumulative size was also higher in non-survivors compared to survivors (mean, 55.9 ± 24.1 mm vs 44.1 ± 29.0, p = 0.006). The results are summarized in Table 1a.

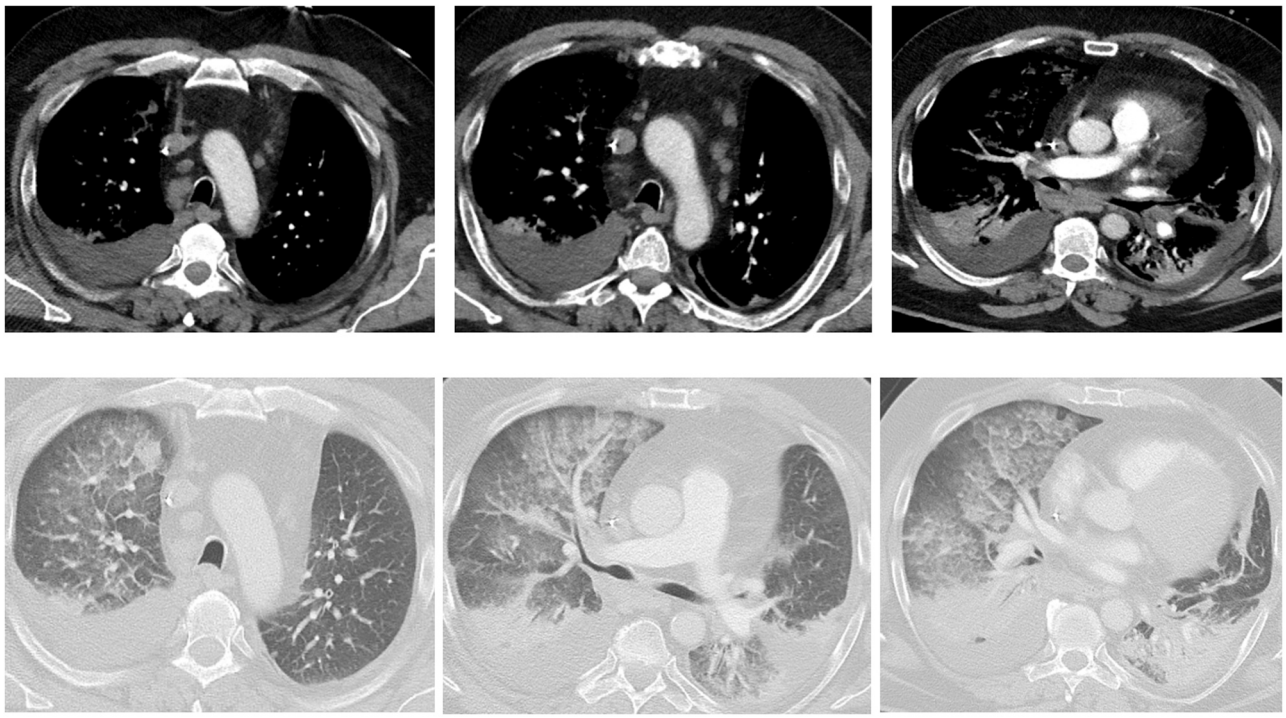

Fig. 1. A representative case of the patient sample with COVID-19 in the upper row in the mediastinal window and in the lower row in the pulmonary window. The mediastinal lymphadenopathy can be appreciated in 8 stations. The cumulative lymph node size is 120 mm and the pulmonary score is 13 in this patient.

Similar results were identified for the need of intubation and need for ICU admission (Table 1 b and c).

Lymphadenopathy and pulmonary affection

The pulmonary severity score differed strongly between patients with thoracal lymphadenopathy and those without (mean 8.9 versus 1.1, $p < 0.001$).

A strong correlation was found between the number of affected lymph node levels and the pulmonary severity score ($r = 0.71$, $p < 0.001$) (Fig. 2a). Similarly, the cumulative size of the lymph nodes was also moderately correlated with the pulmonary severity score ($r = 0.50$, $p < 0.001$) (Fig. 2b).

Prognostic role of thoracal lymphadenopathy

Presence of lymphadenopathy was associated with 30-day mortality, OR = 2.99 (95% CI 1.20 – 7.43), $p = 0.02$ (multivariable regression analysis) (Table 2). The number of affected lymph node levels also influenced 30-day mortality, OR = 1.50(95% CI 1.27 – 1.78),$p < 0.001$. Finally, the cumulative lymph node size was associated with 30-day mortality, OR= 1.02 (95% CI1.008 – 1.03), $p = 0.002$.

Discussion

The present work identified a significant influence of thoracal lymphadenopathy on 30-day mortality in patients with COVID-19. The reported results highlight the prognostic importance of extrapulmonary CT findings in patients with COVID-19 infection.

COVID-19 has a high mortality in patients with an unfavourable course with a reported mortality of up to 20% for patients admitted to the intensive care unit (ICU) [2–6]. As mentioned above, established prognosis parameters are age above 60 years and male sex, shorter period between symptom onset and emergency room presentation [1,6–8]. Moreover, the extension of pulmonary consolidation on CT images harbors also prognostic relevance [2,20,21]. These consolidations are indicative of a disease progression and are most prominent in day 10 of the disease [12].

Thoracal lymphadenopathy is also an imaging finding, which was considered as rare in COVID-19 in the beginning of the pandemic [9]. It was also discussed as an diagnostic sign for bacterial

Table 1
a. Lymph node status in survivors and non-survivors.

	Survivors, n = 124	Non-survivors, n = 53	p-values
Lymphadenopathy, n	86 (69.9%)	44 (84.6%)	0.058
Number of affected levels	2.2 (2.22)	4.0 (2.64)	< 0.001
b. Lymph node status according to the need for Intubation			
	No intubation, n = 86	**Need for intubation, n = 91**	**p-values**
Lymphadenopathy, n	52 (61.2%)	78 (86.7%)	< 0.001
Number of the affected levels	1.8 (2.13)	3.6 (2.46)	< 0.001
Cumulative size of the largest lymph nodes in mm	41.2 (24.68)	53.7 (26.09)	0.001
c. Lymph node status according to the need for ICU Admission			
	No ICU admission, n = 69	**ICU admission, n = 108**	**p-values**
Lymphadenopathy, n	41 (60.3%)	89 (83.2%)	0.001
Number of the affected levels	1.5 (1.88)	3.5 (2.52)	< 0.001
Cumulative size of the largest lymph nodes in mm	38.8 (22.05)	53.2 (27.03)	< 0.001

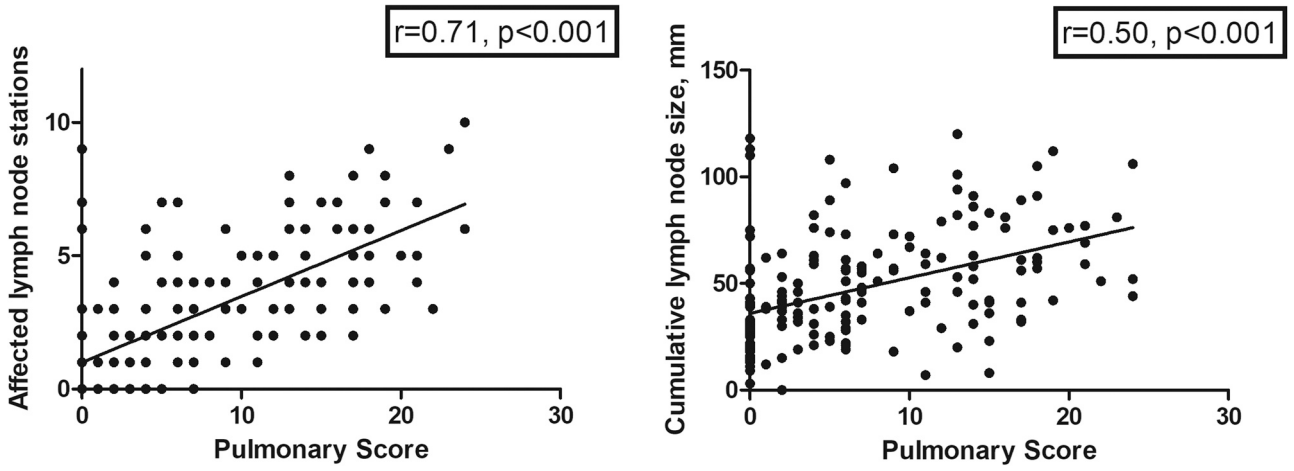

Fig. 2. **a** Correlation between the number of affected lymph node levels and the pulmonary severity score (r = 0.71, p < 0.001).**b** Correlation between the cumulative size of the lymph nodes with the pulmonary severity score (r = 0.50, p < 0.001).

superinfection. Early on, the frequency of mediastinal lymphadenopathy was reported to be only 3.4% [22]. In another meta analysis the frequency ranged from 5% to 28% [14]. Of note, the frequency can differ according to the threshold value of enlargement. A commonly used threshold value was 10 mm in short axis in most studies [14].

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 [23]. Exemplarily, a study employed serological parameters to build a score comprising of white blood cells, C-reactive protein, lymphocyte $\geq 0.8 \times 10^9$/L, and lactate dehydrogenase ≥ 400 U/L. This score was highly accurate to predict survival with a reported area under the curve of 0.95 [23].

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 [17–19].

In a recent meta analysis of CT findings in COVID-19, the time dependence of different CT findings was elucidated [24]. Thoracal lymphadenopathy was more frequently identified in later disease stages with 15% compared to 5% in the early stage [24]. Therefore, the time dependence could be a potential confounder of the present analysis and should carefully be analysed when comparing different study results.

However, in most studies regarding the prognostic relevance of CT findings in COVID19, the CTs were performed at hospital admission to reduce possible bias.

A recent study showed that mediastinal lymphadenopathy is a diagnostic factor in favour for COVID-19 pneumonia compared to non-COVID pneumonia [25]. Sampsonas et al. revealed that mediastinal lymphadenopathy is strongly associated with pulmonary involvement but not with mortality [26].

Qayyum et al. investigated 150 patients with acute COVID-19 and found a frequency of mediastinal lymphadenopathy of 23.2%, which is lower than in the current investigated sample [27]. Moreover, Qayyum et al. observed no association between lymphadenopathy and mortality [27]. Presumably, the case severity was higher in our patient sample and could explain the different results. In another study by Erturk et al., over 52% of patients had lymphadenopathy and correlated significantly with hospital length stay [28].

In another recent Korean study investigating 344 patients, the overall frequency was 15.4% [29]. The presence of mediastinal lymphadenopathy was independently associated with a higher risk of ICU admission (reported odds ratio; 3.25, 95% confidence interval 1.06–9.95) but was not significantly associated with the risk of in-hospital death [29].

Noteworthy, the present analysis could link the prognostic relevance of thoracal lymphadenopathy to the pulmonary involvement, as shown in the multivariable analysis.

Histopathologically, it was shown that the affected lymph nodes show a severe capillary stasis and edema, an increased presence of extrafollicular plasmablasts, mild to moderate plasmacytosis, a dominant population of $CD8^+$ T-cells, and histiocytosis with hemophagocytic activity as a morphological correlate [30]. The importance of the prognostic relevance of the lymphadenopathy could be explained by the affection of the immune system by the disease.

There is need for further meta analysis to harmonize the published results regarding the prognostic role of mediastinal lymphadenopathy in patients with COVID-19. Also, a study to further investigate the complex associations between different prognostic factors in patients with COVID-19 is needed to better stratify patients at risk.

The present study has several limitations to address. First, it is a retrospective study with possible known inherent bias. Second, the patient sample is relatively small caused by the single center design. There might be selection bias, which can have an influence of the present results. Also, the present fatal case rate is rather high caused by the inclusion of first wave patients into the analysis. Therefore, the present results might be not representative for patient samples with a lower mortality rate.

Table 2
Uni- and multivariable regression analysis for prediction of 30-day mortality.

	univariable analysis			multivariable analysis (adjusted for age and gender)		
	OR	**CI 95%**	**p-values**	**OR**	**CI 95%**	**p-values**
Presence of lymphadenopathy	2.37	1.02 – 5.52	0.04	2.99	1.20 – 7.43	0.02
Number of the affected levels	1.35	1.17 – 1.55	< 0.001	1.50	1.27 – 1.78	< 0.001
Cumulative size of the largest lymph nodes	1.02	1.01 – 1.03	0.007	1.02	1.008 – 1.03	0.002

Abbreviations: OR = odds ratio, CI = confidence interval

Conclusions

Thoracal lymphadenopathy comprising of cumulative size and affected levels derived from CT images was associated with 30-day mortality in patients with COVID-19. COVID-19 patients presenting with thoracic lymphadenopathy should be considered as a risk group.

Ethics statement

The present retrospective study was approved by the institutional review board (University of Magdeburg, nr. 25/21).

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Declaration of Competing Interest

The authors have no interest to declare.

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References

[1] Chopra V, Flanders SA, Vaughn V, et al. Variation in COVID-19 characteristics, treatment and outcomes in Michigan: an observational study in 32 hospitals. BMJ Open 2021;11:e044921.
[2] Besutti G, Ottone M, Fasano T, et al. The value of computed tomography in assessing the risk of death in COVID-19 patients presenting to the emergency room. Eur Radio 2021:1–12.
[3] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–9.
[4] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
[5] Fernandes Q, Inchakalody VP, Merhi M, et al. Emerging COVID-19 variants and their impact on SARS-CoV-2 diagnosis, therapeutics and vaccines. Ann Med 2022;54:524–40.
[6] Liu B, Spokes P, He W, Kaldor J. High risk groups for severe COVID-19 in a whole of population cohort in Australia. BMC Infect Dis 2021;21:685.
[7] Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect 2020;81:e16–25.
[8] Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. BMC Infect Dis 2021;21:855.
[9] Kwee TC, Kwee RM. Chest CT in COVID-19: what the radiologist needs to know. Radiographics 2020;40:1848–65.
[10] Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients. AJR Am J Roentgenol 2020;215:87–93.
[11] Machnicki S, Patel D, Singh A, et al. The usefulness of chest CT imaging in patients with suspected or diagnosed COVID-19: a review of literature. Chest 2021;160:652–70.
[12] Li K, Wu J, Wu F, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radio 2020;55:327–31.
[13] Sardanelli F, Cozzi A, Monfardini L, et al. Association of mediastinal lymphadenopathy with COVID-19 prognosis. Lancet Infect Dis 2020;20:1230–1.
[14] Meyer HJ, Wienke A, Surov A. Extrapulmonary CT findings predict in-hospital mortality in COVID-19. A systematic review and meta-analysis. Acad Radio 2022;29:17–30.
[15] Harrison EA, Wu JW. Vaccine confidence in the time of COVID-19. Eur J Epidemiol 2020;35:325–30.
[16] Cook TM, Roberts JV. Impact of vaccination by priority group on UK deaths, hospital admissions and intensive care admissions from COVID-19. Anaesthesia 2021;76:608–16.
[17] Pastorino R, Pezzullo AM, Villani L, et al. Change in age distribution of COVID-19 deaths with the introduction of COVID-19 vaccination. Environ Res 2022;204(Pt C):112342.
[18] El-Sherief AH, Lau CT, Wu CC, et al. International association for the study of lung cancer (IASLC) lymph node map: radiologic review with CT illustration. Radiographics 2014;34:1680–91.
[19] Murray JG, Breatnach E. The American Thoracic Society lymph node map: a CT demonstration. Eur J Radio 1993;17:61–8.
[20] Charpentier E, Soulat G, Fayol A, et al. Visual lung damage CT score at hospital admission of COVID-19 patients and 30-day mortality. Eur Radio 2021;31:8354–63.
[21] Zakariaee SS, Salmanipour H, Naderi N, et al. Association of chest CT severity score with mortality of COVID-19 patients: a systematic review and meta-analysis. Clin Transl Imaging 2022;10:663–76.
[22] Bao C, Liu X, Zhang H, Li Y, Liu J. Coronavirus disease 2019 (COVID-19) CT findings: a systematic review and meta-analysis. J Am Coll Radio 2020;17:701–9.
[23] Zeng Z, Wu C, Lin Z, et al. Development and validation of a simple-to-use nomogram to predict the deterioration and survival of patients with COVID-19. BMC Infect Dis 2021;21:356.
[24] Hassanipour S, Azadbakht O, Dehnavi Z, et al. Meta-analysis: COVID-19 diagnosis in chest CT—master key for radiologists. Egypt J Radio Nucl Med 2021;52:86.
[25] Cömert RG, Cingöz E, Meşe S, et al. Radiological findings in SARS-CoV-2 viral pneumonia compared to other viral pneumonias: a single-centre study. Can J Infect Dis Med Microbiol 2022;2022:2826524.
[26] Sampsonas F, Lagadinou M, Kalogeropoulou C, et al. CTPA imaging findings, beyond pulmonary embolism, in patients with severe Acute respiratory syndrome corona virus-2 infection and their relation to clinical outcome - a single center experience. Eur Rev Med Pharm Sci 2022;26:4520–7.
[27] Qayyum U, Akhtar N, Iqbal M, et al. Mediastinal lymphadenopathy as a predictor of worse outcome in severe covid-19 cases. J Ayub Med Coll Abbottabad 2022;34:321–5.
[28] Erturk SM, Durak G, Ayyildiz H, et al. Covid-19: correlation of early chest computed tomography findings with the course of disease. J Comput Assist Tomogr 2020;44:633–9.
[29] Lee JE, Jeong WG, Nam BD, et al. Impact of mediastinal lymphadenopathy on the severity of COVID-19 pneumonia: a nationwide multicenter Cohort study. J Korean Med Sci 2022;37:e78.
[30] Haslbauer JD, Matter MS, Stalder AK, Tzankov A. Histomorphological patterns of regional lymph nodes in COVID-19 lungs. Pathologe 2021;42(Suppl 1):89–97.