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Cardiothoracic Imaging

Automated quantitative thin slice volumetric low dose CT analysis predicts disease severity in COVID-19 patients

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ABSTRACT

Purpose: This study aimed to identify predictive (bio-)markers for COVID-19 severity derived from automated quantitative thin slice low dose volumetric CT analysis, clinical chemistry and lung function testing.

Methods: Seventy-four COVID-19 patients admitted between March 16th and June 3rd 2020 to the Asklepios Lung Clinic Munich-Gauting, Germany, were included in the study. Patients were categorized in a non-severe group including patients hospitalized on general wards only and in a severe group including patients requiring intensive care treatment. Fully automated quantification of CT scans was performed via IMBIO CT Lung Texture analysis™ software. Predictive biomarkers were assessed with receiver-operator-curve and likelihood analysis.

Results: Fifty-five patients (44% female) presented with non-severe COVID-19 and 19 patients (32% female) with severe disease. Five fatalities were reported in the severe group. Accurate automated CT analysis was possible with 61 CTs (82%). Disease severity was linked to lower residual normal lung (72.5% vs 87%, p = 0.003), increased ground glass opacities (GGO) (8% vs 5%, p = 0.031) and increased reticular pattern (8% vs 2%, p = 0.025). Disease severity was associated with advanced age (76 vs 59 years, p = 0.001) and elevated serum C-reactive protein (CRP, 92.2 vs 36.3 mg/L, p < 0.001), lactate dehydrogenase (LDH, 485 vs 268 IU/L, p < 0.001) and oxygen supplementation (p < 0.001) upon admission. Predictive risk factors for the development of severe COVID-19 were oxygen supplementation, LDH > 313 IU/L, CRP > 71 mg/L, <70% normal lung texture, >12.5% GGO and >4.5% reticular pattern.

Conclusion: Automated low dose CT analysis upon admission might be a useful tool to predict COVID-19 severity in patients.
1. Introduction

The coronavirus disease 2019 (COVID-19) is a contagious disease caused by the SARS-CoV-2 virus with severe pneumonic courses requiring intensive care treatment in up to 21% of patients.\(^1\) The diagnosis of COVID-19 is suggested by computer tomography (CT) of the lung and made by nucleic acid amplification test (NAAT) from oro-/nasopharyngeal swabs upon clinical suspicion.\(^5,6\) Moreover, in the absence of a positive NAAT result, CT may further guide the diagnosis of a COVID-19 pneumonia.\(^7\) Previous studies reported bilateral ground glass opacities (GGO) (68–72%), linear opacities (61%), interlobular (33–37%) or pleural thickening (27–56%), as well as secondary peripheral consolidations (13–32%) to be frequent CT findings in patients with COVID-19.\(^4,11\) These data, however, rely on qualitative and semi-quantitative observations, while lung texture changes on CTs are not quantified in clinical routine.\(^5,8\)

The aim of this study was to assess the usefulness of automated, fully quantitative analysis of thin slice low dose CT thorax scans upon admission in COVID-19 patients to reveal their role in the prediction of disease course along with clinical parameters.

2. Materials and methods

This retrospective study was approved by the Ethics Committee of the Ludwig-Maximilians-University of Munich (#20-618) and conducted at the Departments of Pneumology, Infectious Diseases, Radiology and the Intensive Care Unit (ICU) of the Asklepios Lung Clinic Munich-Gauting, Germany. Demographic data were collected from patient documentation. All patients admitted between March 16\(^{th}\) and June 3\(^{rd}\) 2020 with positive SARS-CoV-2 NAAT from oro-/nasopharyngeal swabs and with CT upon admission were included into the study. Patients that had no CT scan on admission were not considered for those parts of the study concerning CT analysis. The cohort was divided in two groups: the non-severe group including patients treated on normal wards and the severe group including patients requiring high-flow nasal cannula therapy, (non-)invasive ventilation and/or other intensive care treatment and all patients with fatal outcomes. Therapy followed the recommendations of the German Society for Infectious Diseases (DGI) at the time of treatment.\(^12\)

Following the strict regulations provided by the German Radiation Protection Law and the working group “Thoracic Imaging” of the German Society of Radiology (AG DRauE zur Durchführung von Low-Dose-Volumen-HRCT), a dedicated low dose high resolution volumetric CT protocol was similarly used in all examined patients.\(^13\) Thorax thin slice low dose volumetric CT scans were obtained using a 16-slice CT scanner with the following settings: 120 kV and automatic tube current (40 mA - 113 mA); continuous thin sections for quantitative analysis, volumetric acquisition, iterative reconstruction technique; rotation time 0.5 s; section thickness 1.25 mm; pitch 1.375; weight adjusted dose-length-product (DLP) = 35–100 mGy*cm. The resulting computed tomography dose index (CTDI) was 0.78 to 2.91 mGy. The protocol used iterative reconstruction to compensate for the signal-to-noise ratio loss, according to the recommendations of the German Society of Radiology.\(^13\)

The automated quantitative low dose volumetric CT analysis was performed using the IMBIO CT Lung Texture Analysis™ software (IMBIO LLC, 807 Broadway St NE, #350, Minneapolis, MN 55413, USA), a software primarily designed to quantify lung texture changes in diffuse parenchymal lung diseases (DPLD).\(^14\) Herewith, thin sections with medium/soft reconstruction kernel were quantitatively analyzed, following the recommendations of the IMBIO™ software. As the acquisition was done in a volumetric way, continuous thin sections for quantitative analysis were used. HRCT reconstructions were not included in this study.

Analysis results were reviewed by one experienced radiologist who was blinded regarding the patients’ state and identity. All CT scans were carefully checked in order to keep only the scans that were judged to be correctly segmented.

Data are presented as median values and interquartile ranges (IQR). Patient demographics, symptoms and radiological findings were compared between groups using the Mann-Whitney U test or contingency tables and chi-squared test statistics. Statistical significance was assumed for a type I error of \(p < 0.05\). Receiver operating characteristics (ROC) and the Youden index were used to derive cut-off values for the likelihood analysis. Statistical analysis was done using Prism 8.0 (GraphPad, San Diego, CA) and SPPS (Version 25, IBM, Armonk, New York, USA).

3. Results

3.1. Demographics of severe and non-severe COVID-19

Between March 16\(^{th}\) and June 3\(^{rd}\) 2020, 75 patients were diagnosed with a positive NAAT for SARS-CoV-2 from oro-/nasopharyngeal swabs and had CTs upon admission. One out of 75 patients was transferred on admission day to a different hospital after the oro-/nasopharyngeal swab was performed. With no clinical, laboratory and radiological reports available, the patient was considered lost to follow-up. Of the remaining 74 patients, 55 (74%) and 19 (26%) patients were categorized into the non-severe and severe disease group, respectively, with 5 (26%) patients deceased during the hospitalization in the severe group (Fig. 1). Patient demographics are described in Table 1.

3.2. Automated quantitative analysis of CT thorax on admission

Fifty-two out of 55 patients with non-severe disease underwent CT thorax imaging, while 16 out of 19 patients with severe COVID-19 were examined via thoracic CT imaging. The automated CT analysis performed by using the IMBIO CT Lung Texture Analysis™ software
Table 1
Demographics of COVID-19 patients with non-severe and severe disease.

| Demographics                  | Non-severe disease | Severe disease | p-Value |
|-------------------------------|--------------------|----------------|---------|
| Age (years) (median [IQR])    | 59 [48–69]         | 76 [62–81]     | 0.001*  |
| % female patients             | 44% (24/55)        | 32% (6/19)     | 0.356   |
| BMI (kg/m²) (median [IQR])    | 25.3 [22.0–29.8]   | 24.5 [23.3–30.4] | 0.974   |
| Obesity* (%)                  | 24% (12/50)        | 21% (3/14)     | 0.164   |
| Respiratory comorbidities (%) | 35% (19/55)        | 21% (4/19)     | 0.273   |
| Cardiac comorbidities (%)     | 51% (28/55)        | 53% (10/19)    | 0.897   |
| Chronic kidney disease (%)    | 6% (3/55)          | 11% (2/19)     | 0.448   |
| Diabetes mellitus (%)         | 7% (4/55)          | 21% (4/19)     | 0.095   |
| In-hospital stay (days) (median [IQR]) | 9.0 [6.0–12.0] | [8.0–27.0] | 0.008* |
| In-hospital stay ICU (days) [median (IQR)] | 0% | 7 [4.3–37.8] | <0.001* |
| Mortality (%)                 | 26% (5/19)         |               |         |

For comparison of age, BMI and in-hospital stay, the Mann-Whitney U test was used. For the remaining data, the Chi-squared test was used.

* p < 0.05 was considered significant.

revealed a missegmentation rate of 10% (5 of 52 patients) and 13% (2 of 16 patients) in the non-severe and severe groups, respectively (Fig. S1).

Examples for automated CT segmentations by the IMBIO™ software for a non-severe and a severe COVID-19 case are illustrated in Fig. 2 A-B. The percentages of affected lung tissue in the upper, middle and lower lung fields were quantified as shown in Fig. 2 C-D.

A detailed topographical description of the missegmentation events is summarized in the Fig. S2.

3.3. Spatial distribution of lung texture changes in non-severe and severe COVID-19

Residual normal lung parenchyma was inversely associated with disease severity. Increased presence of GGO and reticular pattern were seen in patients with severe disease. In the non-severe group, middle and lower lung fields showed more GGO than upper lung fields. However, GGO in the upper lung fields were significantly associated with severe disease course (2% vs 8.5%, p = 0.014) (Table 2).

3.4. Clinical presentation of non-severe and severe COVID-19

No significant differences of clinical symptoms upon admission between patients developing non-severe and severe COVID-19 were observed (Table S1). The clinical and laboratory parameters upon admission are summarized in Table 2.

Table 2
Comparison of CT thorax findings between the non-severe and severe disease group. Median percentages and quartiles are given. The percentage of normal lung parenchyma was significantly reduced in the severe compared to the non-severe group. Ground glass opacities and reticular areas were significantly more prevalent in the severe compared to the non-severe group. For statistical analysis the Mann-Whitney U test was performed.

| CT-radiological pattern distribution | Non-severe disease n = 47 | Severe disease n = 14 | p-Value |
|-------------------------------------|----------------------------|-----------------------|---------|
| Total lung                          | 87% [77.9–91]             | 72.5% [55.3–86.3]     | 0.003*  |
| Ground glass pattern                | 5% [1–10]                 | 8% [3.0–26.5]         | 0.031†  |
| Reticular pattern                   | 2% [1–6]                  | 8% [2.5–10.5]         | 0.025*  |
| Hyperlucency pattern                | 2% [0.7]                  | 2.5% [0.0–12.5]       | 0.979   |
| Upper field                         |                           |                       |         |
| Normal pattern                      | 91.3% [79.5–95]           | 70.9% [55.1–90.4]     | 0.005†  |
| Ground glass pattern                | 2% [0.3–6]                | 8.5% [2.3–26.3]       | 0.014*  |
| Reticular pattern                   | 1.8% [0.5–4]              | 7.1% [1.3–15.4]       | 0.035*  |
| Hyperlucency pattern                | 0.8% [0.4–8]              | 0.5% [0.0–7.3]        | 0.566   |
| Middle/lower fields                 |                           |                       |         |
| Normal pattern                      | 84.8% [75.3–91.4]         | 68.4% [52.6–78.8]     | 0.003*  |
| Ground glass pattern                | 5.6% [1.0–11.6]           | 8.3% [3.6–27.9]       | 0.089   |
| Reticular pattern                   | 2% [0.9–8.8]              | 7.0% [2.1–12.9]       | 0.041*  |
| Hyperlucency pattern                | 3.1% [0.3–7.1]            | 2.4% [0.3–16.3]       | 0.959   |

† p < 0.05 was considered significant.

Fig. 2. Analysis of lung texture patterns in non-severe and severe COVID-19 based on CT thorax scans. A) Radiological texture analysis per lung field was performed using the IMBIO CT Lung Texture Analysis™ software. B) Lung texture analysis shown for one patient with non-severe COVID-19 and one patient with severe disease with the percentages of normal lung parenchyma, marked in green and abnormal lung parenchyma marked in yellow for ground glass opacities and in orange for reticular pattern. Automated quantification of the lung texture in the upper, middle and lower fields with C) pictograms indicating ground glass opacity pattern localization in patients with non-severe and severe COVID-19, respectively, and D) pictograms of reticular lung texture pattern localization in patients with non-severe and severe COVID-19, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
admission are summarized in Table 3.

### 3.5. Summary of parameters predicting disease severity

CRP, LDH, residual normal lung parenchyma, GGO and reticular pattern in CT on admission showed a predictive value in distinguishing severe COVID-19 from non-severe disease in ROC analyses with an area under the curve (AUC) of 0.776 (p < 0.001), 0.833 (p < 0.001), 0.764 (p = 0.003), 0.690 (p = 0.032) and 0.697 (p = 0.026), respectively.

Specifically, CRP serum levels >71 mg/L and LDH serum levels >313 and >500 IU/L upon admission were associated with a severe COVID-19 course. Moreover, patients with <70% normal lung parenchyma, total GGO >12.5%, and total reticular pattern >4.5% more likely developed a severe course of COVID-19 (Table 4). A serum LDH >500 IU/L upon admission showed the strongest predictive value associated with a 43–47% increase in probability for severe COVID-19, given a pre-test probability of 10–40% for severe disease. Oxygen supplementation, LDH and CRP serum levels upon admission as well as total percentage of GGO appeared as negative predictors for a severe disease course (Table 4).

### 4. Discussion

Thoracic CT analysis represents an important tool in the early diagnosis of COVID-19 pneumonia, with a reported specificity, accuracy and sensitivity ranging from 25 to 56%, 68 to 72% and 95 to 98%, respectively. Even though CT scan cannot accurately differentiate between different subtypes of viral pneumonia, the usefulness of the CT imaging in COVID-19 is justified upon clinical suspicion, in the absence of NAAT tests or even negative NAAT results. In addition, CT adds valuable information related to the localization and spatial distribution of the abnormal lung texture patterns in viral pneumonias.

Table 3  
| Parameters on admission | Non-severe disease (n = 55) | Severe disease (n = 19) | p-Value |
|-------------------------|-----------------------------|------------------------|---------|
| Vital parameters, BGA  |                             |                        |         |
| Body temperature (°C)   | 37.0 [36.4–37.8]            | 37.5 [36.5–37.9]       | 0.395   |
| Heart rate (bpm)        | 88.0 [79.0–95.5]            | 88.0 [82.5–100]        | 0.510   |
| MAP (mmHg)              | 96.7 [86.7–100]             | 88.7 [82.7–102]        | 0.372   |
| HRG (%)                 | 0.21 [0.21–0.21]            | 0.28 [0.24–0.40]       | <0.001* |
| Lactate (mmol/L)        | 1.00 [0.7–1.20]             | 1.20 [1.0–2.20]        | 0.006*  |
| Blood counts            |                             |                        |         |
| Leukocytes (x/µL)       | 6.10 [4.48–7.33]            | 8.00 [6.60–10.10]      |         |
| Neutrophils (x/µL)      | 3.77 [2.90–5.14]            | 6.34 [3.26–8.13]       | 0.025*  |
| Erythrocytes (x/µL)     | 4.60 [4.18–5.10]            | 4.55 [3.88–4.85]       | 0.308   |
| Thrombocytes (x/µL)     | 236 [174–315]               | 214 [134–271]          | 0.242   |
| Clinical chemistry      |                             |                        |         |
| C-reactive protein (mg/L) | 36.3 [9.18–79.3]          | 92.2 [66.7–189]        | <0.001* |
| Procalcitonin (ng/mL)   | 0.06 [0.04–0.10]            | 0.14 [0.07–0.34]       | <0.001* |
| eGFR (ml/min)           | 83.0 [67.8–94]              | 55.5 [42.8–71.5]       | 0.001*  |
| GGT/ALAT (IU/L)         | 28.0 [21.0–40.8]            | 51.5 [36.5–59.3]       | <0.001* |
| Bilirubin (µmol/L)      | 0.44 [0.30–0.64]            | 0.62 [0.46–1.03]       | 0.021*  |
| NT-proBNP (µg/L)        | 102 [45.3–279]              | 477 [162–2081]         | 0.012*  |
| Glucose (mg/dL)         | 102 [92.3–115]              | 125 [110–147]          | 0.001*  |
| Lactate dehydrogenase (IU/L) | 268 [200–354]     | 485 [338–568]          | <0.001* |

Median values and quartiles are given. Laboratory parameters from COVID-19 patients hospitalized on normal wards were compared with those patients with severe COVID-19 course following admission. Leukocytes, % neutrophils, inflammatory parameters, as well as renal, liver, and cardiac function parameters, were significantly elevated in the severe compared to the non-severe group.

* For all comparisons, the Mann-Whitney U test was used.

$p < 0.05$ was considered significant.

Table 4  
| Signs upon admission | Likelihood ratio (LR) | Change in probability of severe disease | X²-test (p-Value) |
|---------------------|----------------------|----------------------------------------|------------------|
|                      | if present | if absent | if present | if absent |                      |
| Clinical            |            |            |            |          |                      |
| Oxygen supplementation |          |            | +37–44% | –6–22% | <0.001* |
| CT-radiological measures |          |            |          |          |                      |
| Normal lung pattern |          |            | +30–40% | –        | <0.001* |
| Ground glass pattern |          |            | –        | –        | <0.013* |
| Ground glass pattern |          |            | +17–29% | –        | <0.049* |
| Reticular pattern   |          |            | +10–20% | –        | <0.008* |

* $p > 0.05$ was considered significant.

Potentially clinically relevant predictive parameters are presented with their likelihood ratio if a sign is present or absent. For practical use, the associated increase or decrease in probability for severe disease in presence or absence of the sign was calculated based on a patient population with a pre-test probability for severe disease between 10 and 40%, as discussed in.

including COVID-19. These findings can provide cues for disease severity. A number of studies investigated the CT-morphological features to predict COVID-19 disease severity. Specifically, some reports highlighted the role of normal (well aerated) lung or GGO in predicting COVID-19 severity. However, the majority of these studies were based on qualitative or semi-quantitative CT analysis, without addressing the potential of a fully automated CT quantification in a sufficient manner.

Our study underlined the usefulness of the automated quantitative analysis of the pathological lung textures by repositioning an automated CT analysis software, which had been specifically designed to detect pathological findings observed in DPLD. In particular, it automatically recognizes ground glass, reticular or hyperlucent pattern and their spatial distribution. A blinded manual examination of all CT scan analysis by an experienced radiologist confirmed a successful applicability of this software in the automated analysis of non-DPLD conditions including COVID-19 atypical pneumonia.

In our study, the lung texture analysis in the CT scans of patients developing severe COVID-19 revealed a significantly decreased percentage of normal (unaffected) lung parenchyma, together with significantly increased percentage of GGO and reticular pattern. Our findings were in accordance with the manual quantification analysis reported by Meiler et al. and semi-quantitative analysis by Francoe et al. who showed that >66% affected lung parenchyma or more than two lobes affected were associated with a less favorable COVID-19 course.

In line with these results, Colombi et al. showed in a semi-quantitative analysis that a total volume of well-aerated lung being less than 73% was associated with an unfavorable prognosis in patients with severe COVID-19 course. In comparison to previous studies, where a semi-automated or only a manual analysis was performed, this study aimed at a fully automated quantitative analysis of thoracic CTs. In accordance with previous results, our study showed abnormal findings including GGO and reticular areas to be more pronounced in lower lung fields, as also common in other pulmonary diseases.

However, due to the retrospective character of our study, multiple limitations have to be considered. First, the analysis was based on a
small cohort with only 5 death events recorded, limiting the statistical power of our analysis. Second, even though CT scans were performed very soon after admission, the precise time interval between the onset of symptoms and the CT examination could not be accurately assessed in all cases. However, based on internal patient documentation, we assumed that most of the patients were admitted early by clinical suspicion or during the first week of disease. Third, three patients in each group did not receive a CT scan. In addition, automated CT quantification was not successful in 5 non-severe and 2 severe COVID-19 patients, after careful blinded review by an experienced, board-certified radiologist. As the segmentation algorithm of the IMBIO™ software was designed on thoracic CTs acquired with a non (ultra) low dose protocol and primarily developed for the analysis of lung texture changes in diffuse parenchymal lung diseases and not for viral pneumonia, a low missegmentation rate by the CT analysis software was expected. Missegmentation errors often included a missegmentation of the trachea or the lung apex, as illustrated in Fig. S2. A possible explanation is that the used CT acquisition protocol was designed to minimize patient’s radiation exposition with DLP values (< 40 mGy•cm) and therefore led to a low signal-to-noise ratio and consecutively to difficulties in finding the topographic limits and structures of the trachea and rib cage. Given the almost similar missegmentation rates (10% vs 13%) in the non-severe and severe groups, respectively and consecutively the balanced, low number of patients excluded from both groups, a statistical misinterpretation of the results seems unlikely to us, however it cannot be excluded.

Taken together, this study presents a new fully automated easy-to-apply quantification of the abnormal lung textures in COVID-19 and its possible impact in the clinical practice. It shows for the first time that the IMBIO™ software primarily designed for analysis of diffuse parenchymal lung disease changes on HR-CT might also aid the risk stratification of COVID-19 patients with low-dose thoracic CTs. This fully automated CT analysis strategy using preexisting software can facilitate the application in clinical routine repurposing a sophisticated thoracic CT analysis software.

5. Conclusions

Our study presents a proof of concept for a automated, quantitative thin slice volumetric low dose CT analysis to support COVID-19 severity prediction using preexisting thoracic CT analysis software. Herewith, we showed that the percentage of normal lung parenchyma, ground glass opacities and reticular pattern on CT upon admission were significantly associated with COVID-19 severity. The findings justify further clinical and radiological studies to precisely define the practical value of quantitative CT-analysis for COVID-19 severity prognosis.

6. Precis

Automated quantitative analysis of residual normal lung, ground glass opacities, and reticular pattern on CT thorax upon admission could be a helpful tool for prediction of COVID-19 severity in patients. Supplementary data to this article can be found at https://doi.org/10.1016/jclinimag.2021.04.008.

Declaration of competing interest

None.

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