Discrimination of pulmonary ground-glass opacity changes in COVID-19 and non-COVID-19 patients using CT radiomics analysis

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A CT-based radiomics model was developed to differentiate COVID-19 from other causes of GGOs.
Classification model for GGO lesions could improve specificity of detecting COVID-19 in a general population.
Using radiomics for novel infectious diseases is an advantage when the initial case is limited.

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ABSTRACT

Purpose: The coronavirus disease 2019 (COVID-19) has evolved into a worldwide pandemic. CT although sensitive in detecting changes suffers from poor specificity in discrimination from other causes of ground glass opacities (GGOs). We aimed to develop and validate a CT-based radiomics model to differentiate COVID-19 from other causes of pulmonary GGOs.

Methods: We retrospectively included COVID-19 patients between 24/01/2020 and 31/03/2020 as case group and patients with pulmonary GGOs between 04/02/2012 and 31/03/2020 as a control group. Radiomics features were extracted from contoured GGOs by PyRadiomics. The least absolute shrinkage and selection operator method was used to establish the radiomics model. We assessed the performance using the area under the curve of the receiver operating characteristic curve (AUC).

Results: A total of 301 patients (age mean ± SD: 64 ± 15 years; male: 52.8 %) from three hospitals were enrolled, including 33 COVID-19 patients in the case group and 268 patients with malignancies or pneumonia in the control group. Thirteen radiomics features out of 474 were selected to build the model. This model achieved an AUC of 0.905, accuracy of 89.5 %, sensitivity of 83.3 %, specificity of 90.0 % in the testing set.

Conclusion: We developed a noninvasive radiomics model based on CT imaging for the diagnosis of COVID-19 based on GGO lesions, which could be a promising supplementary tool for improving specificity for COVID-19 in a population confounded by ground glass opacity changes from other etiologies.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) now officially termed coronavirus disease 2019 (COVID-19) has rapidly spread globally, and on 11th March 2020 was declared a global pandemic by the World Health Organization [1]. As of Aug 15 2020, there have been over 21,000,000 confirmed cases reported in 216 countries [2]. For the diagnosis of COVID-19, next-generation sequencing or real-time reverse transcription polymerase chain reaction methods are used as reference standards [3] but computed tomography (CT) has also been reported to be effective in assisting the early detection of COVID-19 cases [4]. CT imaging appearances of COVID-19...
pneumonia have been previously described [5]. The predominant im-
aging pattern of COVID-19 pneumonia is ground-glass opacity (GGO) in
the lung periphery with occasional consolidation on CT [6]. GGOs are
frequently observed and found to be present in 77%–100% of the
confirmed COVID-19 cases [7–9]. Pure GGO lesions could be seen at
the early stage of COVID-19 pneumonia [5] and were reported to be
the main finding after symptom onset [10]. Chung et al. [11] found GGOs
were observed in 12/21 (57 %) of the patients and one patient had
normal CT at the initial scan, followed by a scan after 3 day showing
disease progression of a new solitary, rounded peripheral GGO.
Although CT has a high sensitivity for detection of COVID-19, the
specificity for COVID-19 was low, particularly in regions of low disease
prevalence. A recent meta-analysis showed a pooled specificity was 37
% for chest CT [12].

Fleischner Society Glossary of Terms for Thoracic Imaging defined
GGO as an area with hazy increased opacity of lung with preserved
bronchial structures and vascular markings [13]. The underlying path-
genesis could be partial displacement of the air, thickening of the
interstitium, increased blood volumes in the pulmonary capillary sys-
tem, partial alveoli collapse, or overlaps of these [14]. For patients with
pure GGO as primary findings in CT images, the identification of
COVID-19 could be confounded by malignancy or other pulmonary in-
festions. Currently, and in the future, it is conceivable that we may see
more COVID-19 pneumonia mixed in with other pathologies of similar
GGO appearances. There will be a need to be able to discriminate be-
tween them. Along with clinical assessment, quantitative imaging may
have a role in improving specificity in identifying GGO caused by
COVID-19 pneumonia.

Radiomics refer to a data-driven methodology that extracts large
amounts of advanced quantitative image-based features [15]. This has
been more commonly applied to cancer, but has also been used to
non-invasively capture lesion heterogeneity effectively for infectious
diseases [16,17]. Peripheral GGO is a common morphological change in
CT images. The classification of patients with similar GGO signs could
provide valuable clinical and diagnostic information. The purpose of this
study is to investigate the use of radiomics analysis in GGOs. We hy-
pothesize that CT radiomics features can be used to improve specificity
for detection of COVID-19, and can discriminate GGO of COVID-19 to
non-COVID-19 patients.

2. Methods

2.1. Patient recruitment

This study was approved by multiple Institutional Review Boards of
Queen Mary hospital (QMH), The University of HK PET CT unit (HKU)
and Pamela Youde Nethersole Eastern (PYNEH) hospital. Patients
informed consent was waived due to the retrospective nature of this
study. The diagram for the flow of participants through the study was
summarized in Supplementary Fig. 1. Case group: data were screened
between 24/01/2020 to 31/03/2020 2020 from QMH and PYNEH.
Patients with laboratory-confirmed COVID-19 by reverse transcription
polymerase chain reaction were included, and their initial CT scans were
retrieved. Control group: data were screened between 04/02/2012 and
31/03/2020 from HKU. Patients with reported GGOs in the radiological
report were included in this study. A board-certified radiologist with
fellowship training in cardiothoracic imaging (V.V., with 10 years
experience) then reviewed cases and included cases that have similar
ground glass opacity appearances. For patients in the control group
collected after December 2019, underwent strict clinical +/- laboratory
assessment prior to entering the unit to exclude potential infection with
COVID-19. Clinical details such as history and clinical assessment was
obtained as standard for diagnosis, in conjunction with histological and
laboratory tests if they were available. Patients with incomplete data
were excluded. A total of 301 patients (age mean ± SD: 64 ± 15 years;
male: 52.8 %) were enrolled in this study. The images acquisition details
are listed in Supplementary Method.

With a balanced distribution of the clinical outcome (COVID-19),
recruited patients were separated into the training and testing sets at a
proportion of 3:1 by a stratified randomization approach.

2.2. Contour of the regions of interest (ROI)

All CT images were obtained and reviewed by two radiologists
jointly (C.X. and V.V., of 2 and 10 years’ experience respectively)
independently without clinical information to avoid bias. Patients with
GGOs fulfilling the definition from the Fleischner Society Glossary of
Terms for Thoracic Imaging [13] on lung window (~600 Hounsfield unit
[HU] level, 1500 HU width) were included for further analysis. GGOs
were manually contoured in one representative slice by the ITK-SNAP
software [18]. We excluded the large vessels and arteries when draw-
ing the ROI. GGOs appearing as nodules were also excluded. A test-retest
study was conducted in a subset of 30 patients with ROI contoured by
two radiologists from the training set for the determination of feature
robustness. Features with intraclass correlation coefficients above 0.80
were included for further analysis.

2.3. Feature extraction

Radiomics features were extracted using PyRadiomics [19]. The
resampled voxel sizes were set to 1 × 1 mm² pixels for standardization.
Defined radiomics features were extracted from original and wavelet
filtered images. Wavelet filtration (high pass filter and low pass filter)
filtered original images directionally with x and y directions respec-
tively, resulting in 4 combinations of decompositions. Filtered images
could present more detailed information of the images from different
orientations. Additional details are specified in Supplementary Method.

2.4. Feature harmonization

As CT images were collected from different hospitals using different
acquisition and reconstruction parameters, radiomics features were first
harmonized using ComBat method to reduce the batch effect [20].

2.5. Feature selection

Feature selection was conducted in two steps. First, the top 100
features correlated with the outcome analyzed by univariate analysis
were selected. Second, regularized multivariate logistic regression with
the least absolute shrinkage and selection operator (LASSO) penalty was
applied [21]. The LASSO algorithm could select features with a coeffi-
cient of larger than zero by the optimal λ.

2.6. Model construction

Because of limited access to the COVID-19 data across different
medical centers, labelled positive cases are insufficient at the early stage
of disease outbreak, which could lead to data imbalance problems. The
uneven distribution of positive and negative cases could result in pre-
dictions skewed towards the negative class. To solve this problem, we
adopted re-sampling techniques during the training process. An open-
source solution for automatic calculations of different re-sampling
techniques was adopted for the selection of optimal resampling tech-
niques [22].

A radiomics score (Rad-score) was calculated for each patient using
the Radial Basis Function kernel support vector machine (SVM) with
selected features. According to the optimal prediction threshold of the
radiomics model in the training set, each patient was divided into
different risk groups (COVID-19 and non COVID-19) by the diagnostic
possibility.
2.7. Statistical analysis

We used Python version 3.7. for statistical analyses. Categorical variables were compared using Chi-squared test/ Fisher’s exact test, while continuous variables were compared using Kruskal-Wallis test. We used the area under the curve of the receiver operating characteristic curve (AUC), accuracy, sensitivity and specificity to assess the prediction performance and their 95% confidence intervals were provided. The optimal prediction threshold is defined by Youden index [23]. The calibration performance was shown by calibration plots. Clinical usefulness was evaluated by decision curve analysis. A two-tailed P value of less than 0.05 was considered statistically significant.

3. Result

3.1. Patient baseline characteristics

Fig. 1 depicts the workflow processes. A total of 301 patients were enrolled in this study, including 33 in the case group. The remaining 268 were collected as the control group, including 136 non-COVID19 pneumonia, 48 malignant tumors, and 84 benign lesions of indeterminate nature. No significant differences between the training and testing datasets in terms of COVID-19 events (p = 0.44) were found. The baseline characteristics of the patients are shown in Table 1.

3.2. Model evaluation

A total of 474 radiomics features were extracted (102 original and 372 with wavelet filtration). In the test-retest experiment, 417 features demonstrated intraclass correlation coefficients above 0.80 and were included for further analysis (Supplementary Table 1). After LASSO, this reduced the feature number to 13.

The Adaptive Synthetic oversampling technique was used for the data re-sampling process in the training set [22]. The radiomics model using linear regression comprised of 13 selected features achieved an AUC of 0.905, accuracy of 89.5 %, sensitivity of 83.3 %, specificity of 90.0 % in the independent testing set. Imaging features have previously been shown to correlate with the pathogenesis of viral infections and could indicate the viral pathogens [24]. Recent COVID-19 studies based on CT images were predominantly of diagnostic [25–28] and prognostic models [29,30]. Diagnostic models mainly focused on detecting COVID-19 pneumonia in suspicious patients with symptoms (body temperature, and signs and symptoms). Most of the previous studies were performed at the image level for the diagnosis of COVID-19. Texture features have been shown to be predictive of COVID-19 infection in early literature using a combination of machine learning and deep learning techniques with quantitative imaging analysis, with a few adopting radiomics analysis. Yue et al. [30] demonstrated that CT radiomics models showed feasibility and accuracy for predicting hospital stay in COVID-19 patients. Barstugan et al. [25] reported a prediction model built based on the textural feature of Grey-Level Size Zone Matrix could achieve a classification accuracy of 99.7 %, sensitivity of 97.6 % and specificity of 99.7 %. This study used a square-shaped patch rather than image segmentation comparing diseased vs normal lungs in same COVID-19 patients. This differed from our study as we focused our comparison on GGO of COVID-19 patients compared to other etiologies with a separate control group. Our study is

| Characteristic | Case group (COVID-19) | Control group (non COVID-19) |
|---------------|----------------------|-----------------------------|
| Age (mean ± SD) | 33 ± 22              | 65 ± 13                     |
| Sex (n)       | Male: 18, Female: 15  | Male: 141, Female: 127      |
| Disease (n)   | Pulmonary infection (COVID19): 33, Pulmonary infection (other causes): 0, Pulmonary adenocarcinoma: 0, Benign lesions of indeterminate nature: 0 | Pulmonary infection (COVID19): 0, Pulmonary infection (other causes): 136, Pulmonary adenocarcinoma: 48, Benign lesions of indeterminate nature: 84 |
| Signs (%)     | Fever (>37.5 °C): 59 %, Cough: 47 %, Dyspnea: 24 %, Chest Pain: 12 %, Vomiting: 3 %, Diarrhea: 12 % | Fever (>37.5 °C): 25 %, Cough: 13 %, Dyspnea: 18 %, Chest Pain: 5 %, Vomiting: 2 %, Diarrhea: 2 % |

Note—COVID-19 = coronavirus disease 2019.

4. Discussion

Our proposed radiomics risk screening method achieved good prediction performance with an AUC of 0.905, accuracy of 89.5 %, sensitivity of 83.3 %, specificity of 90.0 % in the independent testing set. Imaging features have previously been shown to correlate with the pathogenesis of viral infections and could indicate the viral pathogens [24]. Recent COVID-19 studies based on CT images were predominantly of diagnostic [25–28] and prognostic models [29,30]. Diagnostic models mainly focused on detecting COVID-19 pneumonia in suspicious patients with symptoms (body temperature, and signs and symptoms). Most of the previous studies were performed at the image level for the diagnosis of COVID-19. Texture features have been shown to be predictive of COVID-19 infection in early literature using a combination of machine learning and deep learning techniques with quantitative imaging analysis, with a few adopting radiomics analysis. Yue et al. [30] demonstrated that CT radiomics models showed feasibility and accuracy for predicting hospital stay in COVID-19 patients. Barstugan et al. [25] reported a prediction model built based on the textural feature of Grey-Level Size Zone Matrix could achieve a classification accuracy of 99.7 %, sensitivity of 97.6 % and specificity of 99.7 %. This study used a square-shaped patch rather than image segmentation comparing diseased vs normal lungs in same COVID-19 patients. This differed from our study as we focused our comparison on GGO of COVID-19 patients compared to other etiologies with a separate control group. Our study is
the first to provide a classification model for COVID-19 diagnosis on CT imaging for the diagnosis of COVID-19 based on GGO lesions, which could be a promising supplementary tool for improving specificity for COVID-19 in a population confused by ground glass opacity changes from other etiologies.

Note—For wavelet filtration, “H” and “L” represent high pass filter and low pass filter on the x and y directions. GLCM = Gray Level Co-occurrence Matrix, GLRLM = Gray Level Run Length Matrix, GLSZM = Gray Level Size Zone Matrix, NGTDM = Neighboring Gray Tone Difference Matrix.

5. Conclusion

In conclusion, we developed a noninvasive radiomics model based on CT imaging for the diagnosis of COVID-19 based on GGO lesions, which could be a promising supplementary tool for improving specificity for COVID-19 in a population confused by ground glass opacity changes from other etiologies.

Author statement

This original study has not been published elsewhere and has not been submitted simultaneously for publication elsewhere. All the authors have approved the final version of the manuscript for this submission.
Originality

This original study has not been published elsewhere and has not been submitted simultaneously for publication elsewhere.

Ethical approval

This study was approved by multiple Institutional Review Boards in the study. Patients informed consent was waived due to the retrospective nature of this study.

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CRediT authorship contribution statement

Chenyi Xie: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing. Ming-Yen Ng: Investigation, Data curation, Writing - review & editing. Jie Ding: Software, Formal analysis, Writing - review & editing. Siu Ting Leung: Investigation, Data curation, Writing - review & editing. Christine Shing Yen Lo: Investigation, Data curation, Writing - review & editing. Ho Yuen Frank Wong: Investigation, Data curation, Writing - review & editing. Varut Vardhanabhuti: Conceptualization, Methodology, Supervision, Writing - original draft, Writing - review & editing, Project administration.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejro.2020.100271.

References

[1] P. Zhou, X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, H.R. Si, Y. Zhu, B. Li, C. L. Huang, H.D. Chen, J. Chen, Y. Lao, H. Guo, R.D. Jiang, M.Q. Liu, Y. Chen, X. R. Shen, X. Wang, X.S. Zheng, K. Zhao, Q.J. Chen, F. Deng, L.L. Liu, B. Yan, F. X. Zhao, Y.Y. Wang, G.F. Xiao, Z.L. Shi, A pneumoni outbreak associated with a new coronavirus of probable bat origin, Nature 579 (7798) (2020) 270–273.
[2] G.W.H. Organization, Coronavirus disease (COVID-19) outbreak situation, 2020 (Aug 16 2020), https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
[3] G.W.H. Organization, Coronavirus Disease (COVID-19) Technical Guidance: Laboratory Testing for 2019-nCoV in Humans, 2020 (Accessed Aug 15 2020), https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance.
