Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Mediastinal lymphadenopathy in patients with severe COVID-19

CT has a leading place in the management of patients with coronavirus disease 2019 (COVID-19). Mediastinal lymph node enlargement is not considered a typical CT feature of COVID-19, and only 6% of patients admitted to hospital for COVID-19 had lymphadenopathy.[1] This observation is concordant with previous studies in Chinese populations.[2,3] However, our experience in critically ill patients with COVID-19 in France seems to be different.

15 patients with positive RT-PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were admitted to our intensive care unit (ICU) for acute respiratory failure on March 27, 2020. Among them, nine patients were under invasive mechanical ventilation and one patient was also under extracorporeal membrane oxygenation, whereas two patients were under high-flow nasal canula oxygenation. CT examination was performed in nine patients, with typical ground-glass opacities, reticulation, or consolidation features observed in all patients, as described in a recent expert consensus statement on chest CT findings related to COVID-19.[4] The median number of days between onset of symptoms and CT scans was 7 days (IQR 6–8). Lymphadenopathies greater than 10 mm in the short axis were observed in six (66%) of the nine patients. Notably, several patients had voluminous lymphadenopathies, particularly in the subcarinal location, measuring up to 30 mm in the short axis (appendix). Invasive microbiological samples were assessed to rule out bacterial or fungal coinfection in all patients. Similarly, no patient had any haemophagocytic lymphohistiocytosis, neoplasia, or systemic disease.

See Online for appendix

Thus, lymphadenopathy was more common in our French cohort of ICU patients than previously reported. To our knowledge, highly enlarged mediastinal lymph nodes have not been described in patients with COVID-19. Most reports were not specifically concerning critically ill patients, so disease severity could probably explain this discrepancy, as suggested by Li and colleagues.[5] Further studies are needed to better characterise the CT features of patients with COVID-19, in order to establish a possible link between the presence of specific radiological signs and the severity of the disease. Pending such studies, lymphadenopathy should not be considered an atypical feature of COVID-19, especially when we have seen that mediastinal lymph nodes are very large in our critically ill patients.

We declare no competing interests.

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Association of mediastinal lymphadenopathy with COVID-19 prognosis

Xavier Valette and colleagues[1] reported a high (66%) prevalence of mediastinal lymphadenopathy in 15 patients with COVID-19 admitted to their intensive care unit (ICU), an approximately 11-fold discrepancy with systematic reviews reporting pooled prevalence of 3·4%[2] and 5·4%.[3] This topic deserves further investigation, especially considering that small sample sizes imply large confidence intervals.

We retrospectively reviewed 410 patients with COVID-19 (including 288 male and 122 female patients; median age of all patients 68 years [IQR 57–78]) who underwent CT at emergency department admission in three hospitals in Lombardy, Italy (Fondazione Poliambulanza Istituto Ospedaliero, Brescia; ASST Crema, Ospedale Maggiore, Crema; ASST Santi Paolo e Carlo, Ospedale San Paolo, Milan), from Feb 21 to March 18, 2020, during the pandemic peak in Lombardy. 76 patients had mediastinal lymphadenopathies (ie, lymph nodes with a short-axis diameter >1 cm), giving a prevalence of 19% (95% CI 15–22).

Whereas our CT examinations were done at emergency department admission, Valette and colleagues' data[1] derive from patients in the ICU. Thus, our lower lymphadenopathy prevalence could be explained by the lower severity illness of our patients. However, 60 (15%) patients in our cohort were admitted to the ICU, of whom only 15 (25%, 95% CI 14–36) had lymphadenopathies at emergency department admission (appendix).

Valette and colleagues[1] hypothesised that disease severity could probably explain the discrepancy between previous data and their ICU population. After applying the Bonferroni correction for multiple comparisons to our series of patients (obtaining a p value threshold of 0·003, above which p values were not significant), we found no significant differences between patients with and without lymphadenopathies in terms of sex, age, history of cancer, non-invasive ventilation or ICU admission during hospitalisation, length of hospital stay,

laboratory findings, and CT features such as parenchymal involvement and disease progression, both assessed according to the classification by Bernheim and colleagues[4] (appendix). However, lymphadenopathies at admission were significantly more frequent in patients with a crazy paving pattern on CT than in those without (33 [31%] of 106 *vs* 43 [14%] of 304, p<0·001) and in patients who died during hospitalisation than in those who were discharged (37 [27%] of 136 *vs* 39 [14%] of 274, p=0·001; appendix).

Although invasive microbiological samples were not available for our patients (so we cannot exclude bacterial or fungal coinfections), our lymphadenopathy prevalence was lower than that reported by Valette and colleagues[1] but three times higher than estimates for other populations.[2,3,5] We therefore agree in defining lymphadenopathy as a "not-atypical" feature of COVID-19. Furthermore, our data suggest that lymphadenopathy may be considered a predictor of a worse outcome. The pathophysiological meaning of this finding in relation to host response to virus infection and the possibility to use this information in the clinical management of patients with COVID-19 remain to be investigated.

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Pooling of samples for testing for SARS-CoV-2 in asymptomatic people

The ongoing coronavirus disease 2019 (COVID-19) pandemic is a substantial challenge for health-care systems and their infrastructure. RT-PCR-based diagnostic confirmation of infected individuals is crucial to contain viral spread because infection can be asymptomatic despite high viral loads. Sufficient molecular diagnostic capacity is important for public health interventions such as case detection and isolation, including for health-care professionals.[1]

Protocols for RNA RT-PCR testing of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became available early in the pandemic, yet the infrastructure of testing laboratories is stretched and in some areas it is overwhelmed.[2] We propose a testing strategy that is easy to implement and can expand the capacity of the available laboratory infrastructure and test kits when large numbers of asymptomatic people need to be screened. We introduced the pooling of samples before RT-PCR amplification, and only in the case of positive pool test results is work-up of individual samples initiated, thus potentially substantially reducing the number of tests needed.

Viral load during symptomatic infection with SARS-CoV-2 was investigated by Zou and colleagues.[3] To analyse the effect of pooling samples on the sensitivity of RT-PCR, we compared cycle threshold (Ct) values of pools that tested positive with Ct values of individual samples that tested positive.

We isolated RNA from eSwabs (Copan Italia, Brescia, Italy) using the NucliSens easy MAG Instrument (bioMeriéux Deutschland, Nürtingen, Germany) following the manufacturers' instructions. PCR amplification used the RealStar SARS-CoV-2 RT-PCR Kit 1.0 RUO (Altona Diagnostics, Hamburg, Germany) on a Light Cycler 480 II Real-Time PCR Instrument (Roche Diagnostics Deutschland, Mannheim, Germany) according to the manufacturers' instructions.

Our results show that over a range of pool sizes, from four to 30 samples per pool, Ct values of positive pools were between 22 and 29 for the envelope protein gene (E-gene) assay and between 21 and 29 for the spike protein gene (S-gene) assay. Ct values were lower in retested positive individual samples (figure A, B). The Ct values for both E-gene and S-gene assays in pools and individual positive samples were below 30 and easily categorised as positive. Ct value differences between pooled tests and individual positive samples ($Ct_{pool} - Ct_{positive\ sample}$) were in the range of up to five. Even if Ct values of single samples were up to 34, positive pools could still be confidently identified (figure C, D). Sub-pools can further optimise resource use when infection prevalence is low. Generating a pool of 30 samples from three sub-pools of ten samples can reduce retestings.

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