Protective Reactive Thymus Hyperplasia in the COVID-19 Acute Respiratory Distress Syndrome

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Abstract

Background. COVID-19 (COVID) patients can develop acute respiratory distress syndrome associated or not with sepsis, coagulopathy and visceral injuries. While thoracic CT-scans are routinely performed in the initial evaluation of patients with severe pulmonary forms, thymus involvement and reactivation have not been investigated so far.

Methods. In this observational study, we systematically scored the thymus enlargement and the lung involvement, using CT-scans, in all adult patients admitted in ICU for COVID or any other cause (control group) in one center between March and April 2020. Initial biological investigations included nasal detection of SARS-CoV-2 ribonucleic acid detection by positive polymerase chain reaction (PCR). In a subgroup of 24 patients with different degrees of pulmonary involvement and thymus hypertrophy, plasma cytokines concentrations were measured and mature T-cell export from the thymus was estimated simultaneously by PCR quantification of T-cell receptor excision circles (TRECs).

Results. Eighty-seven patients were studied: 50 COVID patients and 37 controls. Non-atrophic or enlarged thymus was more frequent in COVID patients than in controls (66% vs. 24%, p<0.0001). Thymus enlargement in COVID patients was associated with more extensive pulmonary involvement score on CT-scans 4 [3-5] vs. 2 [1.5-4], p=0.01, but lower mortality (8.6% versus 41.2%, p<0.001). Other factors associated with mortality were age, lymphopenia, high CRP and co-morbidities. COVID patients had higher concentrations of IL-7: 6.00 [3.72-9.25] vs. 2.17 [1.76-4.4] pg/mL; p=0.04, and higher thymic production of new lymphocytes: TRECS ratio = 2.88 [1.98-4.51] vs. 0.23 [0.15-0.60]; p=0.004. This thymic production was also correlated to the CT-scan thymic score (r = 0.38, p=0.03) and inversely correlated to the lymphocyte count (r=0.56, p=0.007).

Conclusions. In COVID patients, thymus enlargement was frequent and associated with increased T-lymphocytes production that appears a beneficial adaptation to virus-induced lymphopenia. The loss of thymic reactivation might contribute to worse prognosis.

Trial registration: NA

Introduction

Five months after the beginning of the coronavirus 2019 pandemic (COVID-19) due to the virus identified as SARS-CoV2, an increasing number of studies has markedly improved our knowledge of its epidemiology and illustrated the large spectrum of clinical consequences of the infection. Although a large proportion of infected people remains asymptomatic or develops a more or less severe flu-like syndrome, some patients requires hospitalization [1, 2]. A fraction of them can develop severe forms, the severe acute respiratory syndrome (SARS) being the most frequent, associated or not with acute myocardial injury, sepsis, coagulopathy and other organs injury [3-5]. In France, the infection fatality ratio is on average 0.53%, ranging from 0.001% in individuals under 20y to 8.3% in patients >80y [6]. Several studies have identified clinical and biological risk factors for death, including age, gender, co-morbidities

(such as obesity, diabetes, hypertension), D-dimer concentration, low lymphocyte count, high C-reactive protein [2, 7]. Although the mortality is low, given the scale of the pandemics, the actual number of deaths is considerable. It is thus of primary importance to elucidate the pathophysiological mechanisms, which determine the gravity of the COVID-19 in some individuals, and which can necessitate specific therapeutic approaches.

Recent investigations highlighted the role of increased pro-inflammatory cytokines (cytokine storm) [8, 9], impaired type-I interferon response [10] and functional exhaustion of anti-viral lymphocytes [11, 12] in the severity of COVID-19. These findings, similar to those reported in previous pathogenic human coronavirus epidemics due to SARS-CoV-1 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), reflect the shift from a protective regulated inflammatory response against the virus to pathogenic dysregulated inflammation [13]. In this context, during the initial evaluation of adult patients admitted to intensive care unit (ICU) for COVID-19-associated SARS, we noticed a previously unreported marked thymus enlargement at CT-scan in some individuals. Although thymus continues to generate new T lymphocytes into adult years, it undergoes progressive physiological involution with age [14, 15]. Enlargement of the thymus region, particularly among senior adults, is mostly observed in autoimmune conditions, tumours, or reactive thymus hypertrophy in response to profound lymphopenia [16], which is common in patients with severe COVID-19. However, thymic volume is not directly related to the extent of thymic function, which consists in producing and exporting mature T-cells into the blood.

The objective of this study was to score the thymus enlargement in all thoracic CT-scans performed in patients admitted in our ICU in March and April 2020, and to compare the scores of COVID-19 patients with others. The clinical status, thymus function and outcome were then compared according to this scoring.

Methods

Patients

This observational study was conducted in all 87 adult patients hospitalised in the Intensive Care Unit (ICU) of the Clinique Ambroise Paré (Neuilly, France) from the beginning of March to the end of April 2020. During this period of time, this ICU, which under normal circumstances principally treats patients admitted for cardiovascular diseases, contributed to the national French program aimed at enhancing the hospitalization capacity in ICU of severely affected SARS-CoV-2-infected patients. Fifty patients with suspected or confirmed COVID-19 (COVID group) were admitted for fever and respiratory distress. The SARS CoV2 infection was based on ribonucleic acid detection by positive polymerase chain reaction (PCR) and/or clinical history associated with the notion of a plausible contamination by a proven infected contact. For some patients, the diagnosis of COVID-19 was performed after the admission. The other 37 patients admitted for other reasons were investigated as controls.

According to French National Regulation, systematic written informed consent was requested to all patients on admission, for the potential anonymous use in clinical research studies of clinical and para-clinical data obtained during hospitalization.

Thoracic CT-scans

Thoracic CT-scans were performed for the initial evaluation of pulmonary conditions at admission. Specific settings were used to examine the thymus area. All images were independently reviewed and classified by two radiologists, then by the two in case of discordance. Classification of pulmonary parenchymal images is shown in Table 1. The thymus aspect was also classified in 3 groups. Patients displaying fatty atrophy of the thymus (the most common in senior adults) were classified as the subgroup 0. Patients with homogeneous non-fatty thymus, commonly observed in young adults, or fatty thymus area associated with micro-nodules, were classified as the subgroup A. Patients showing various levels of thymus hyperplasia or pseudo-tumoral thymus represented the subgroup B (Figure 1).

Table 1
CT-scan classification of COVID-19-associated pneumopathy

0	Absent or minor pulmonary parenchymal changes
1	Limited ground-glass opacities
2	Bilateral ground-glass opacities < 50% of pulmonary parenchyma
3	Idem 2, with superimposed interlobular / intralobular septal thickening “crazy paving”
4	Bilateral ground-glass opacities > 50% of pulmonary parenchyma
5	Idem 4, with superimposed “crazy paving”
6	Idem 5, with pulmonary fibrosis

Laboratory procedures

Initial clinical laboratory investigation included a complete blood count, serum biochemical tests, including liver and kidney function, creatine kinase, lactate dehydrogenase, and electrolytes, fibrinogen and C reactive protein (CRP), and a coagulation profile. Nasal swabs were used for the detection of SARS-CoV-2 ribonucleic acid by quantitative PCR (following the procedure recommended by the manufacturer).

Plasma IL-7 concentration was also measured using the U-plex technique (Meso Scale Diagnostics, Rockville, Maryland) according to manufacturer instructions.

The capacity of the thymus to export mature T-cells into the blood stream was estimated the same day in 24 hospitalized patients including 18 COVID patients and 6 controls with different degrees of pulmonary involvement and thymus hypertrophy. The procedure, conducted as described previously [17], is based on

PCR quantification of T-cell receptor excision circles (TRECs) in peripheral blood mononuclear cells [18]. Two types of TRECs were quantified : DJβTRECs (T1), and sjTRECs (T2) [18]. As TRECs do not duplicate during cell division, their frequency in a given T-cell population is inversely proportional to the number of cell divisions subsequent to TREC generation. The amount of T2 in peripheral blood mononuclear cells reflects the amount of “recent thymic emigrants” in the blood. Measurement of T2 frequency alone may be an imperfect estimate of thymic production in situations where T-cell homeostasis is modified such as systemic infections. In this context, the measurement of T2/T1 ratio in peripheral blood cells, which reflects the intra-thymic proliferative history of T-cell precursors, is a better estimate of thymic output [19].

Statistical analysis

Descriptive statistics were used to present baseline characteristics for the total population and for the various groups. Normality of continuous data was assessed using a Shapiro-Wilk test. Continuous variables are presented as mean±SD or median [25-75% interquartile range] according to their distribution and categorical variables are presented as the number of patients in each category and the corresponding percentages. Missing data were not replaced. Quantitative variables were compared using Student *t* test or Mann–Whitney *U* test according to the normality of their distribution. Categorical variables were compared using Pearson tests. Kruskall-Wallis tests were used to compare three groups. Bivariate (correlation coefficient) or multivariate (logistic regression) analyses were performed to determine the relationships between the variables. JMP software was used for statistical analysis and a value of $p<0.05$ was considered to be statistically significant.

Results

Descriptive analysis

Thymus persistence or enlargement (subgroups A and B) was more frequent in the COVID group (66% vs. 24%, $p<0.0001$), except in patients over 80 y (Figure 2, $p<0.05$). Descriptive analysis of the two groups at time of the first CT-scan is summarized in Table 2.

COVID patients with persistent or enlarged thymus were younger than patients with normal thymic fatty atrophy, and displayed, on average, more severe pulmonary involvement: 4 [3-5] vs. 2 [1.5-4], $p=0.01$, Figure 3. They were also less frequently hypertensive, developed less frequently renal failure and had a lower mortality rate (8.6% versus 41.2%, $p<0.001$, Figure 4). Sex ratio, lymphopenia and D-dimer concentration were not different among the subgroups.

Table 2
Descriptive analysis of investigated patients BMI: body mass index; COPB: chronic obstructive pulmonary disease; CRP: C protein reactive. Mech. = Mechanical. *, **, ***: p<0.05, 0.001, 0.0001, respectively.

	Control (n=37)			COVID (n=50)		
Thymus enlargement	0 (n=28)	A (n=4)	B (n=5)	0 (n=17)	A (n=14)	B (n=19)
Demographics						
Sex ratio (M)	21 (75)	3 (75)	3 (60)	11 (65)	12 (86)	14 (74)
Age. yr	64.3 ± 13.9	79.5 ± 13.1	71.2 ± 13.8	75.4 ± 12.6	59.3 ± 12.7	55.3 ± 16.2***
BMI. kg/m^2	25.7 [22.5-27.5]	27.1 [23.5-30.4]	23.3 [20.7-32.5]	26.8 [25.0-30.3]	26.7 [24.2-29.8]	29.3 [26.0-35.7]
Medical history						
Hypertension	13 (46)	1 (25)	2 (40)	13 (76)	5 (36)	8 (42)*
Diabetes	3 (11)	-	1 (20)	3 (18)	3 (21)	5 (26)
COPB	4 (14)	1 (25)	1 (20)	5 (29)	1 (7)	1 (5)
Renal failure	3 (11)	1 (25)	-	9 (53)	1 (7)	1 (5)**
Cancer	6 (21)	1 (25)	3 (60)	2 (12)	1 (7)	2 (11)
Smoking status:						
Never	21 (75)	3 (75)	4 (80)	14 (82)	11 (79)	15 (79)
Former	3 (11)	-	-	3 (18)	3 (21)	3 (16)
Current	4 (14)	1 (25)	1 (20)	-	-	1 (5)
Type of admission						
COVID suspicion	1 (4)	-	-	14 (82)	13 (93)	13 (68)
CT-Scanner only	3 (11)	-	-	1 (6)	-	-
Cardiovascular medicine	11 (39)	3 (75)	2 (40)	1 (6)	-	3 (16)
Cardiac surgery	8 (29)	-	3 (60)	-	-	2 (11)
Spine surgery	-	-	-	-	1 (7)	-
Uro-digestive surgery	5 (18)	-	-	-	-	1 (5)
Chronic Dialysis	-	1 (25)	-	1 (6)	-	-

Biological data						
Hemoglobin (g/L)	12.0 ± 2.8	12.0 ± 1.9	10.2 ± 1.6	11.1 ± 2.1	13.1 ± 1.7	11.5 ± 1.7
Leukocytes ($x10^9$/L)	8.7 [7.1-10.0]	11.0 [9.3-13.4]	8.1 [7.4-12.7]	5.6 [3.9-8.9]	6.9 [5.4-8.1]	8.5 [5.1-10.1]
Lymphocytes ($x10^9$/L)	1.2 [0.8-1.7]	1.3 [0.9-2.4]	1.1 [0.4-5.2]	0.6 [0.5-1.5]	0.8 [0.7-1.0]	1.0 [0.5-1.5]
Monocytes ($x10^9$/L)	0.8 [0.5-1.0]	0.9 [0.7-1.2]	0.5 [0.3-0.9]	0.5 [0.3-0.9]	0.5 [0.3-0.7]	0.7 [0.3-0.9]
Lymphocytes (%)	14.3 [9.8-23.2]	10.3 [9.5-21.8]	16.7 [4.3-40.7]	15.0 [7.1-24.9]	12.2 [10.1-18.0]	13.1 [7.2-19.6]
Monocytes (%)	9.1 [7.2-10.8]	8.6 [6.0-10.4]	5.9 [2.5-11.3]	10.0 [7.3-11.4]	8.2 [5.8-9.1]	7.6 [5.5-10.7]
Fibrinogen (g/L)	5.1 [2.7-6.0]	6.2 [5.9-6.5]	4.6 [2.0-7.1]	4.8 [4.3-10.0]	5.9 [5.8-7.0]	6.9 [5.8-7.3]
D-dimer (ng/mL)	1527 [1213-4240]	816 [521-1111]	-	1092 [814-1813]	1066 [878-2250]	1256 [825-2040]
CRP (mg/L)	21 [2-67]	55 [19-79]	44 [11-113]	128 [62-218]	115 [64-180]	86 [33-220]
Clinical data						
Mechanical ventilation	12(43)	-	4(80)	6(35)	5(36)	9(45)
Length of stay (days)	14 ± 12	4 ± 3	16 ± 14	12 ± 12	17 ± 13	14 ± 10
Mech. ventilation (days)	0.7 ± 2.2	-	1.8 ± 2.4	11.1 ± 3.2	15.4 ± 3.8	5.2 ± 2.8
Secondary pneumopathy	-	-	-	2 (12)	2 (14)	2 (11)
Deceased	3 (11)	-	-	7 (41)	1 (7)	1 (5)**

Prognostic factors

Overall, factors associated with mortality (univariate analysis, Table 3) in the COVID group were older age, hypertension, associated chronic obstructive pulmonary disease, renal failure, lower thymus CT-score, severe lymphopenia and high CRP. The multivariate analysis selected only two independent predictors of death: age (OR=0.82 [0.64-0.94], p=0.0005), and lymphocyte count (OR=1.01 [1.00-1.02], p<0.0001).

Table 3
Mortality in the COVID group, univariate analysis. BMI: body mass index; COPB: chronic obstructive pulmonary disease; CRP: C protein reactive.

	Survivors (n=41)	Non-survivors (n=9)	p
Clinical data			
Age.(y	60.1 ± 2.3	78.9 ± 5.1	0.002
Height (cm)	174 ± 2	169 ± 6	0.18
Weight (kg)	88.1 ± 3.5	77.3 ± 7.8	0.20
BMI (Kg/m^2)	28.9 ± 1.0	27.3 ± 2.2	0.49
Sex ratio (M/F)	31-déc	07-févr	0.73
Hypertension (%)	42	89	0.01
Diabetes (%)	20	33	0.42
Smoker (%)			0.76
Never	89	79	
Former	11	19	
Current	-	2	
COPD (%)	7	44	0.003
Renal failure (%)	14	56	0.006
Cancer (%)	11	13	0.82
CT-Scan findings			
Thymus CT-Score 0 (%)	24	78	0.009
Lung CT-scan score	3 [2-4]	4 [2-5]	0.38
Data at admission			
PaO2/FIO2	290 ± 31	264 ± 51	0.65
Hemoglobin (g/100ml	12.0 ± 0.3	10.6 ± 0.7	0.06
Leukocytes ($x10^9/L$)	7.6 ± 0.6	7.9 ± 1.3	0.79
Lymphocytes ($x10^9/L$)	1.3 ± 0.2	0.4 ± 0.4	0.05
Lymphocytes (%)	18 ± 2	8 ± 3	0.009
Monocytes ($x10^9/L$)	0.63 ± 0.05	0.49 ± 0.11	0.27
Monocytes (%)	11 ± 1	7 ± 3	0.37

Fibrinogen (g/L)	6.34 ± 0.4	7.10 ± 1.0	0.46
D-dimer (ng/mL)	4579 ± 1158	4510 ± 2577	0.48
CRP (mg/L)	111 ± 15	206 ± 32	0.01

Inflammation analysis

We found significantly higher concentrations of IL-7 in the plasma of COVID patients as compared to controls: 6.00 [3.72-9.25] vs. 2.17 [1.76-4.04] pg/mL; p=0.04; suggesting that this cytokine might contribute to thymus reactivation. Interestingly, IL-7 values were rather well related to lymphocyte counts in both COVID patents and controls (r=0.38 and r=0.64; p=0.05 and p=0.08, respectively).

As expected, T2 TRECs values decreased as a function of age in both COVID patients and controls. They were also grossly correlated with the CT-scan thymic score (r=0,42, p=0.04). The T2/T1 ratio was higher in COVID patients than in controls, particularly in older individuals, consistent with enhanced thymic production of new lymphocytes (2.88 [1.98-4.51] vs. 0.23 [0.15-0.60], p=0.004; Figure 5). Interestingly, the T2/T1 ratio was also correlated to the CT-scan thymic score (r = 0.38, p=0.03) and inversely correlated to the lymphocyte count (r=0.52, p=0.009).

Discussion

We found that 66% of the COVID patients had thymus reactivation, associated with more severe pulmonary involvement but less mortality (8.6% versus 41.2%). These findings were not mentioned in previous reports of COVID-19-associated features, despite common thoracic CT-scan examination in patients with pulmonary symptoms. The emergency context in which scans of patients hospitalized in intensive care for severe forms of COVID-19 pneumonia were performed have probably contributed to underestimate changes occurring in the thymic area. Indeed, analysis of the CT-scan images of pulmonary parenchyma requires specific settings (for example, adjustment of grey levels), which are not suitable for mediastinum analysis causing a lack of contrast between the various mediastinal tissues.

In adults, thymus hyperplasia is rare and can be observed in a limited number of pathological conditions: auto-immune diseases such as myasthenia gravis [20] and Graves-Basedow disease [21], after high-dose chemotherapy associated or not with autologous stem cell transplantation [22]-[23], in lymphopenic human immunodeficiency virus (HIV)-infected patients with maintained naïve T-cell counts [24] or after antiretroviral therapy [25]. In the setting of severe T-cell depletion, caused by HIV infection or cytoreductive transplant or chemotherapy regimens, thymus hyperplasia is critical for the restoration of peripheral T-cell populations [23].

In patients with severe forms of COVID-19, intense lymphopenia is frequent. In our study it was associated with overall reduced survival and inversely correlated with the intra-thymic proliferation of T-cell precursors. Together, these data indicate that the enhancement of thymic function observed in COVID

patients is a beneficial adaptation to SARS-CoV-2-induced lymphopenia, associated with an increased thymic production. This adaptation, at least partly triggered by enhanced IL-7 levels, appears to decline in patients above 80y, likely contributing to the higher mortality observed among more senior patients. A similar progressive reduction of T-cell precursors with age was reported after autologous peripheral blood stem cell transplant [23], and in a systematic study of 1000 healthy individuals showing that age and sex strongly affect thymic function [26]. Moreover, while potential genetic factors are currently under investigation in COVID-19 patients who develop severe forms despite the absence of risk factors, it should be noted that precursor T-cell proliferation is genetically determined [27],[26]. Surprisingly, contrarily to previous observations in lymphopenic patients, IL-7 plasma level was proportional to blood lymphocyte counts in COVID patients. This observation indicates that during acute SARS-Cov2 infection, high IL-7 plasma levels were not due to its low consumption by T-cells as previously suggested [28], but most probably originate from an active overproduction, as previously evidenced in acute SIV-infection in rhesus macaques [29]. Contrary to thymic production, the actual size of thymus in CT-scans of patients belonging to subgroups A and B of thymus classification was not inversely correlated with lymphopenia. Nodular and/or minimal areas of hyperplastic thymus might be sufficient to restore an adequate amount of peripheral lymphocytes.

The finding that the pulmonary involvement of COVID-19 patients quantified by the CT-scan score was significantly higher in patients with thymus enlargement, appears contra-intuitive respective to data and hypotheses above. A plausible explanation of this apparent paradox is that in patients with an “activated productive” thymus, the influx of immune cell into infected lungs is different from that occurring in patients with “non-reactive” thymus. This hypothesis is supported by a recent study in which cells from broncho-alveolar lavage fluid of COVID-19 patients were characterized using single-cell RNA sequencing. Monocyte-derived inflammatory macrophages were found in severe forms of COVID-19 pneumonia contrasting with the clonal expansion of CD8+ T-cell effectors in mild cases, indicative of a role of CD8+ T-cells of the adaptive immune response in the clearance of SARS-CoV-2 [30].

This observational study, conducted in an emergency context, has some limitations. TRECs could only be evaluated in patients who were still hospitalized; some immunologic investigationq in the blood or broncho-alveolar lavage fluid had not been anticipated, and patient follow up was limited in time. Prospective studies will be necessary to further characterize the role of thymic function in the control of SARS-CoV-2 infection and the involved molecular and cellular mechanisms.

Conclusion

In response to SARS-CoV-2 infection, thymic reactivation is frequent and seems to be a good prognostic factor since it would testify of lymphopenia-compensating mechanisms contributing to an efficient adaptive immune response within the lungs. CT-scan examination of the thymic area with appropriate settings is recommended in all COVID-19 patients with pulmonary involvement.

Declarations

Ethics approval and consent to participate.

According to French National Regulation for retrospective studies, systematic written informed consent was requested to all patients on admission, for the potential anonymous use in clinical research studies of clinical and para-clinical data obtained during hospitalization.

Consent for publication:

Not applicable

Data availability.

Should the paper be accepted, all data and materials would be available from the corresponding author (PS) and from a repository

Competing interests:

All authors declare no competing interest with this study.

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Author contributions:

P.C. made the initial observation, performed and analyzed all CT-scans; H.R., A. C-C., B.C.-D.M. performed TRECs and IL-7 analysis; C.N. compiled and organized all patient data, R.C. supervised immunological investigations and reviewed the manuscript; P.S. initiated and coordinated the study, performed statistical analyses and reviewed the manuscript; S.M. coordinated the study and wrote the manuscript.

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Authors' information:

RC and his team developed the method for estimating the thymic function through quantification of T-cell receptor excision circles.

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Figures

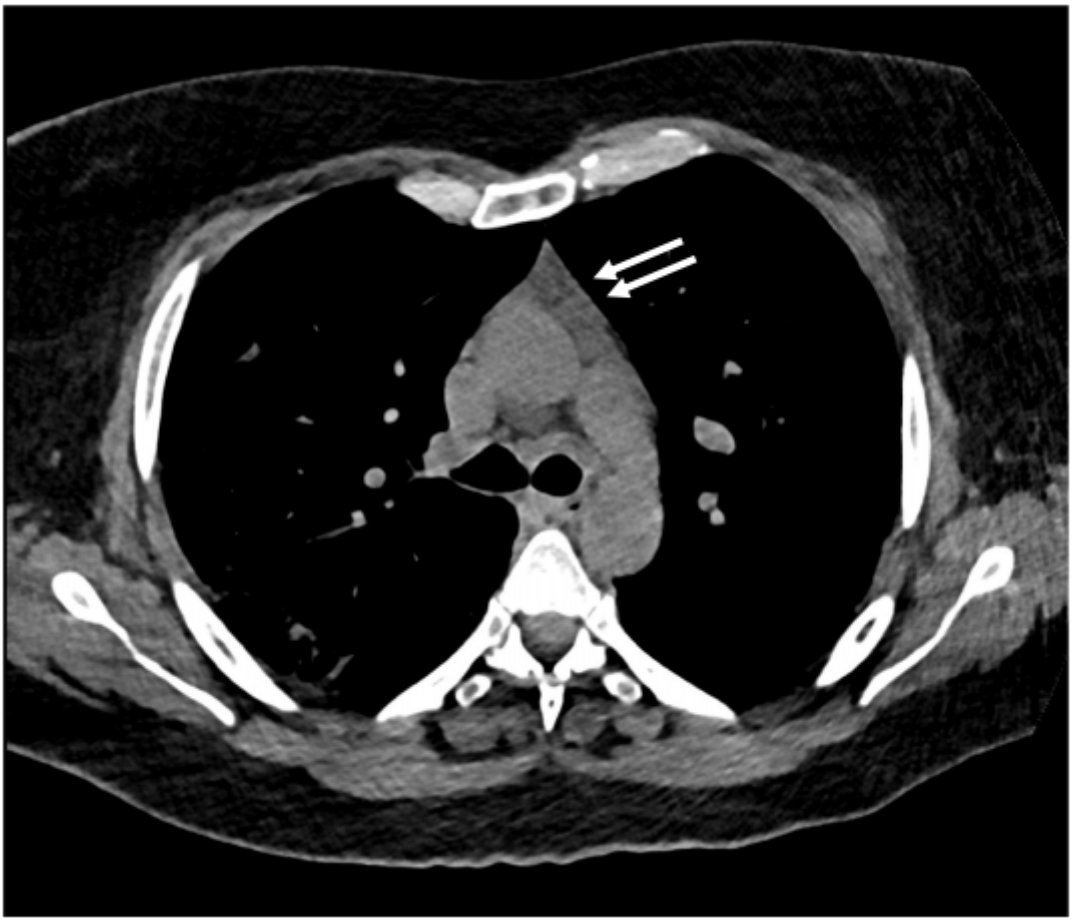

Figure 1

Thymus hyperplasia indicated by arrows

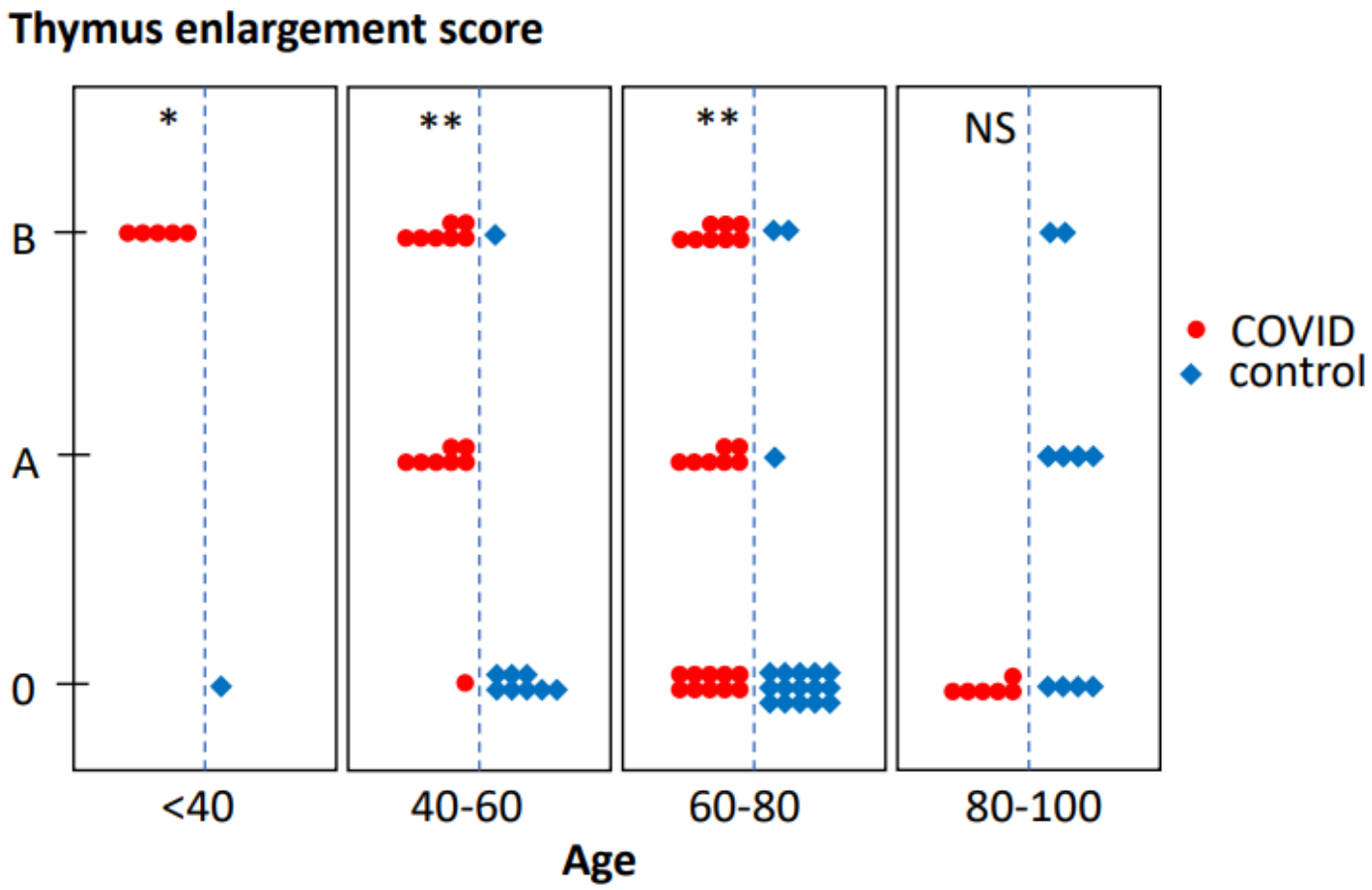

Figure 2

Thymic enlargement in COVID and control groups according to age patients. *, **: p<0.05, p<0.001, respectively.

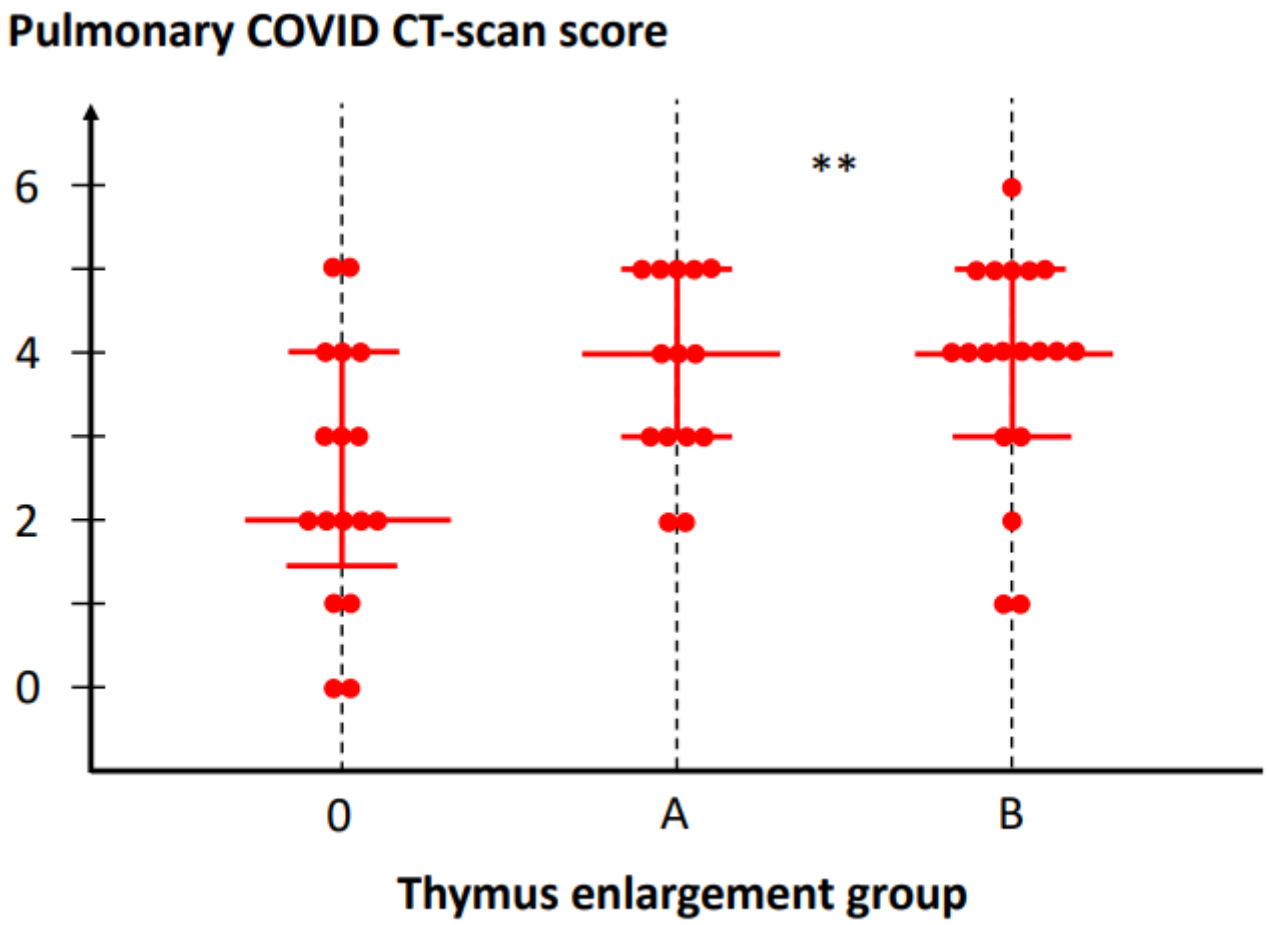

Figure 3

Lung damage in COVID patients, according to thymus enlargement. Median values with the 25-75% interquartile ranges are shown; ** p=0.01 between groups.

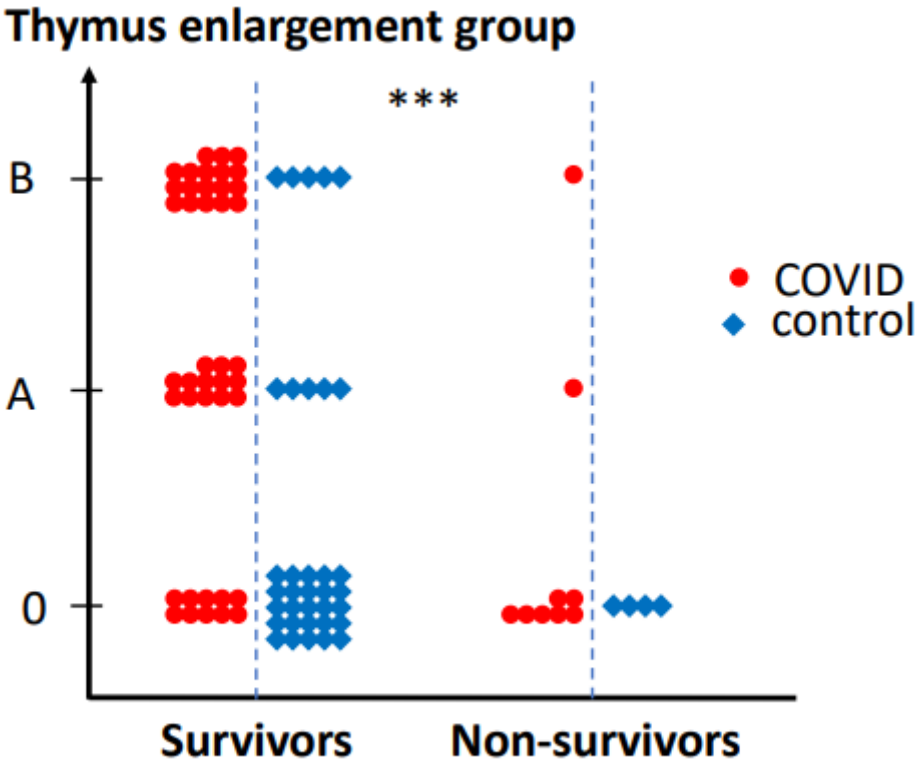

Figure 4

Survival as a function of thymic reactivation. *** p<0.0001 between groups.

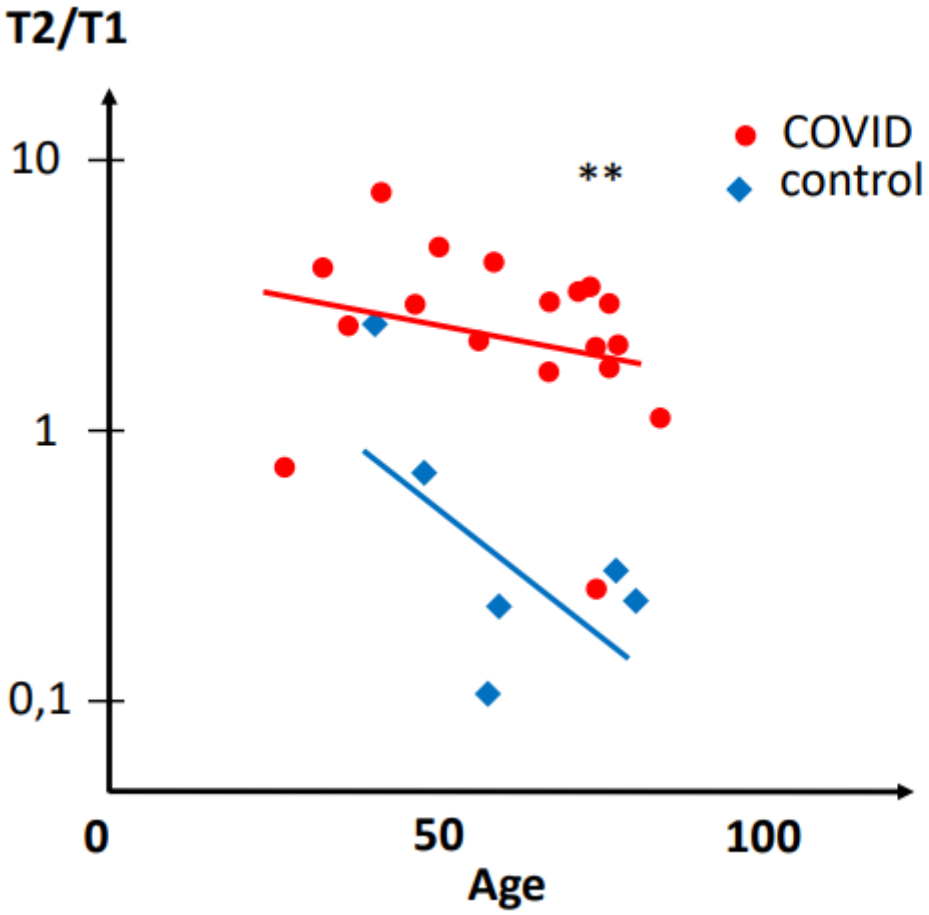

Figure 5

Thymic function (estimated though T2/T1) in COVID patients; ** p<0.001 between groups.

Supplementary Files

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- GraphAbstract.pdf