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Thymic Hyperplasia and COVID-19 Pulmonary Sequelae: A Bicentric CT-Based Follow-Up Study

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Abstract: This study aimed to investigate the role of the thymus in influencing long-term outcomes of COVID-19 by comparing the thymic appearance in patients with and without COVID-19 pulmonary sequelae at chest computed tomography (CT). A total of 102 adult patients previously hospitalized for COVID-19 underwent a follow-up chest CT three months after discharge. Pulmonary sequelae and thymic appearance were independently assessed by two experienced radiologists. The thymus was detectable in 55/102 patients (54%), with only 7/55 (13%) having any kind of pulmonary sequelae, compared to 33 out of 47 (70%, $p < 0.001$) in patients without thymic visibility, as confirmed in age-stratified analysis and at logistic regression analysis, where thymic involution had a 9.3 odds ratio (95% CI 3.0–28.2, $p < 0.001$) for the development of pulmonary sequelae. These results support the hypothesis that thymic reactivation plays a protective role against adverse long-term outcomes of COVID-19.

Keywords: COVID-19; pulmonary sequelae; thymus hypertrophy; COVID-19 chest fibrotic changes

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1. Introduction

The global impact of the COVID-19 pandemic has extended far beyond the acute phase of the illness, with a growing recognition of persistent consequences in survivors and an intense exploration of the intricate facets of the immune system and its short-term and long-term responses to the SARS-CoV-2 virus.

As with previous acute coronavirus infections such as severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), that are associated with the development of persistent lung changes attributable to fibrosis [1–3], fibrotic lung changes have also emerged as a significant and challenging manifestation in COVID-19 [4]. As individuals recover from the acute infection, a subset experiences the symptomatic correlations of fibrotic lung changes, characterized by the abnormal accumulation of scar tissue in the pulmonary parenchyma. Direct viral injury, host immune response, and barotrauma are the three causes of lung injury associated with COVID-19, and each can potentially result in long-term lung damage [5]. Chest computed tomography (CT) has emerged as a key diagnostic tool in identifying lung injury and revealed a spectrum of fibrotic patterns, ranging from subtle interstitial changes to more pronounced lung fibrosis [6]. Ground-glass opacities, consolidation, bronchiectasis, parenchymal bands, and reticular patterns are

among the hallmarks captured by CT imaging, painting a detailed picture of the evolving lung pathology [5] that is the subject of ongoing research [7].

Recognized clinical and biological risk factors for long-term post-COVID-19 alterations include the severity of COVID-19 pneumonia, female sex, obesity, socioeconomic deprivation, and pre-existing disease [8–10]. However, the role of other favoring or protecting variables still needs to be assessed, as the early identification of protective and risk factors may potentially alter the course of post-COVID-19 recovery.

Among the various components of the immune system, the thymus emerges as a central player: the T cell-mediated immune response plays a key role in the defense against viral infections and its importance has been progressively recognized as one of the determining factors in COVID-19 outcomes [11,12]. Thymic involution in adults is correlated with age [13], and thymic hyperplasia, indicative of increased T lymphocyte production, is known to be a detectable manifestation of the immune system's response to autoimmune disorders and virus-induced lymphopenia. Conversely, the lack of thymic activity and reactivation has been linked to a worse prognosis in COVID-19 patients [14,15]. Its association with the severity of lung involvement during the acute phase of the infection has seen contrasting reports in acute care settings [14,15]: however, to the best of our knowledge, it has never been investigated in the context of follow-up after hospital discharge.

This study aimed to evaluate the relationship between the presence of thymic hyperplasia and of pulmonary sequelae in discharged COVID-19 patients who underwent a 3-month CT follow-up.

2. Materials and Methods

This multicenter retrospective study was performed at Centro Diagnostico Italiano (Center 1) and at Fatebenefratelli Hospital—ASST Fatebenefratelli Sacco (Center 2), both in Milan, Italy, after approval from the local Ethics Committee (Comitato Etico Sacco Area 1, Milan, Italy; study ID 2417, approved on 29 September 2021). We included consecutive adult patients who were previously hospitalized for RT-PCR-proven SARS-CoV-2 infection, did not need invasive ventilatory support during hospitalization, and were referred by a pulmonologist for a 3-month follow-up unenhanced chest CT—performed between January 2021 and September 2021—due to post-COVID symptoms.

In both centers, chest CT scans were executed on the same scanner (Somatom Definition Flash, Siemens Healthineers), with the following acquisition parameters: reference kV, 120; reference mAs, 150 (with automated tube current modulation); rotation time, 0.5 s; collimation, 128 × 0.6 mm; pitch value, 1; scan direction, craniocaudal, and reconstructed as follows: for lung, slice thickness of 0.75 mm with reconstruction spacing of 0.5 mm; for mediastinum, slice thickness of 3 mm and reconstruction spacing of 1 mm.

Image datasets were transferred to the picture archiving and communication system for assessment with lung parenchyma and mediastinal windows and were independently reviewed by two radiologists with 10 and 16 years of experience in chest imaging. Their inter-reader reliability for the assessment of pulmonary sequelae and thymic appearance was evaluated with Cohen's κ, interpreted according to the Landis and Koch scale [16]. After inter-reader reliability analysis, the remaining discrepancies were solved by consensus.

Pulmonary sequelae were graded (pulmonary sequelae score) on a 0–6 scale [14] as follows: grade 0 corresponded to absent or minor pulmonary parenchymal abnormalities; 1 to limited ground-glass opacities; 2 to bilateral ground-glass opacities, involving less than 50% of pulmonary parenchyma; 3 to grade 2 but with the coexistence of inter/intralobular septal thickening, resulting in a crazy paving appearance; 4 to bilateral ground-glass opacities involving more than 50% of pulmonary parenchyma; 5 to grade 4 with the coexistence of crazy paving aspects; and 6 to grade 5 with associated pulmonary fibrosis. The categories of pulmonary sequelae were then dichotomized as category 0 (corresponding to absent or minor pulmonary parenchymal alterations) versus categories 1–6 (from limited ground-glass opacities to bilateral diffusion with associated pulmonary fibrosis).

Thymic fat involution was graded (T score) on a four-point scale [17] as follows: 1, well-recognizable thymus characterized by predominantly soft-tissue attenuation, similar to the muscle density; 2, approximately 50% thymus with fatty involution and 50% characterized by soft-tissue-attenuated thymus; 3: predominantly fatty thymus; 4, complete thymus fatty replacement, without any identifiable soft tissue component in the anterior mediastinum. The thymus classification was dichotomized as categories 1–3 (from no fat infiltration—i.e., thymic hyperplasia—to fat infiltration >50%) versus category 4 (complete thymic fat involution) (Figures 1–3).

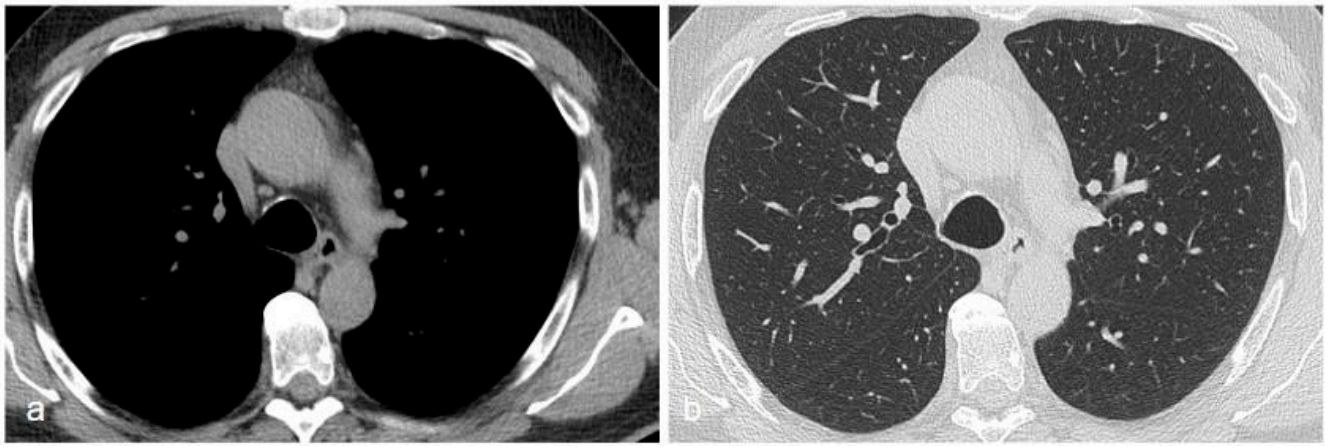


Figure 1. (**a**) Mediastinal window showing a grade 2 T score, with approximately 50% of the thymus with fatty involution and 50% characterized by soft-tissue-attenuated tissue. No pulmonary alterations are visible on the lung parenchyma CT reconstruction (**b**).

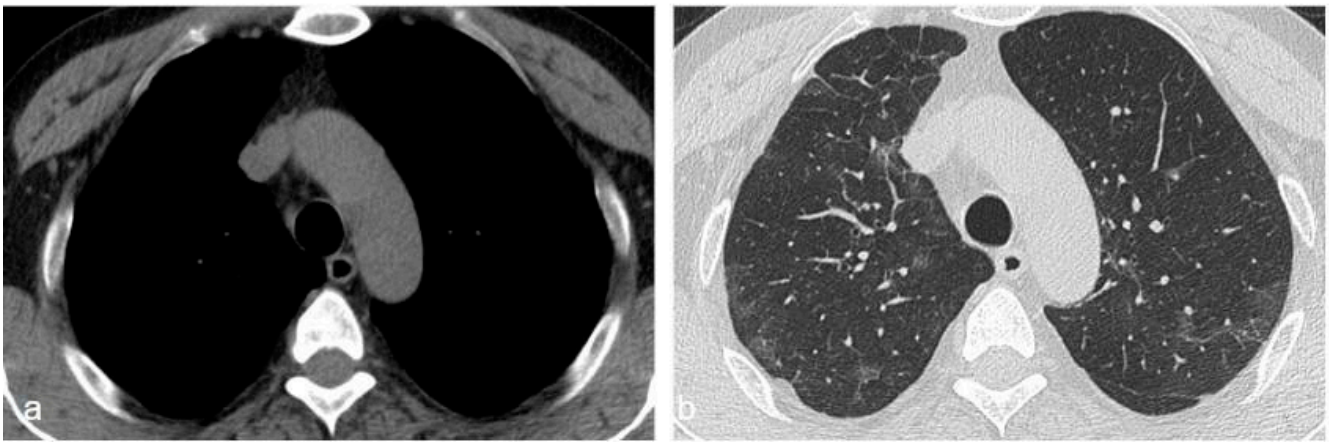


Figure 2. Complete fatty involution of the thymus, visible in the mediastinal window (**a**). With the lung parenchyma reconstruction algorithm (**b**), a grade 5 pulmonary sequelae score is visible as bilateral ground-glass opacities involving more than 50% of pulmonary parenchyma with the coexistence of crazy paving aspects.

Using SPSS (version 26.0; IBM), direct comparisons of thymic status and pulmonary sequelae were performed with Fisher's exact test, while age-stratified comparisons (considering age 45 as a cut-off for commonly observed thymic involution) were performed with the Cochran–Mantel–Haenszel test. After univariate binary logistic regression, multivariable binary logistic regression was used to calculate adjusted odds ratios (ORs) for the development of pulmonary sequelae, with 95% CI.

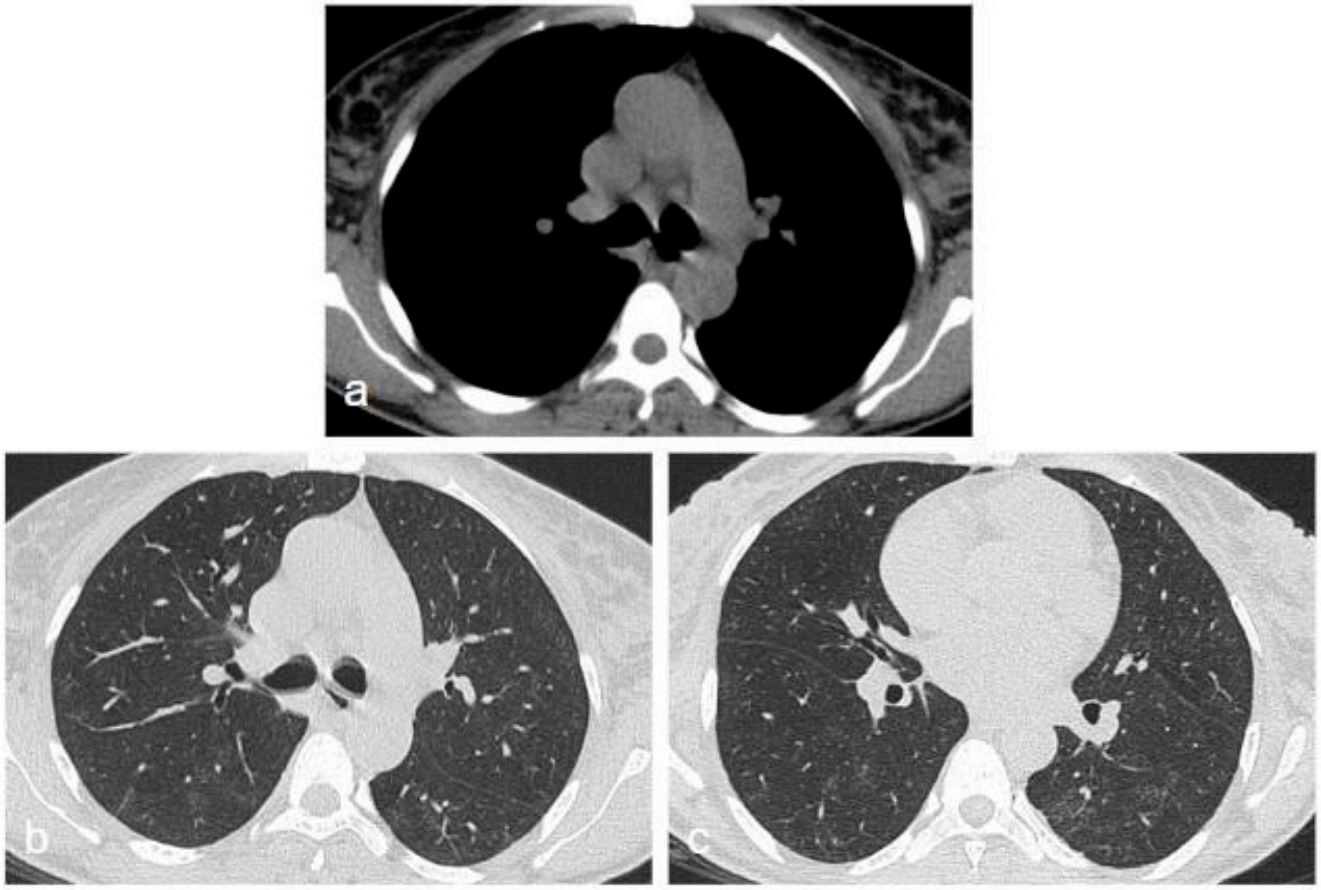
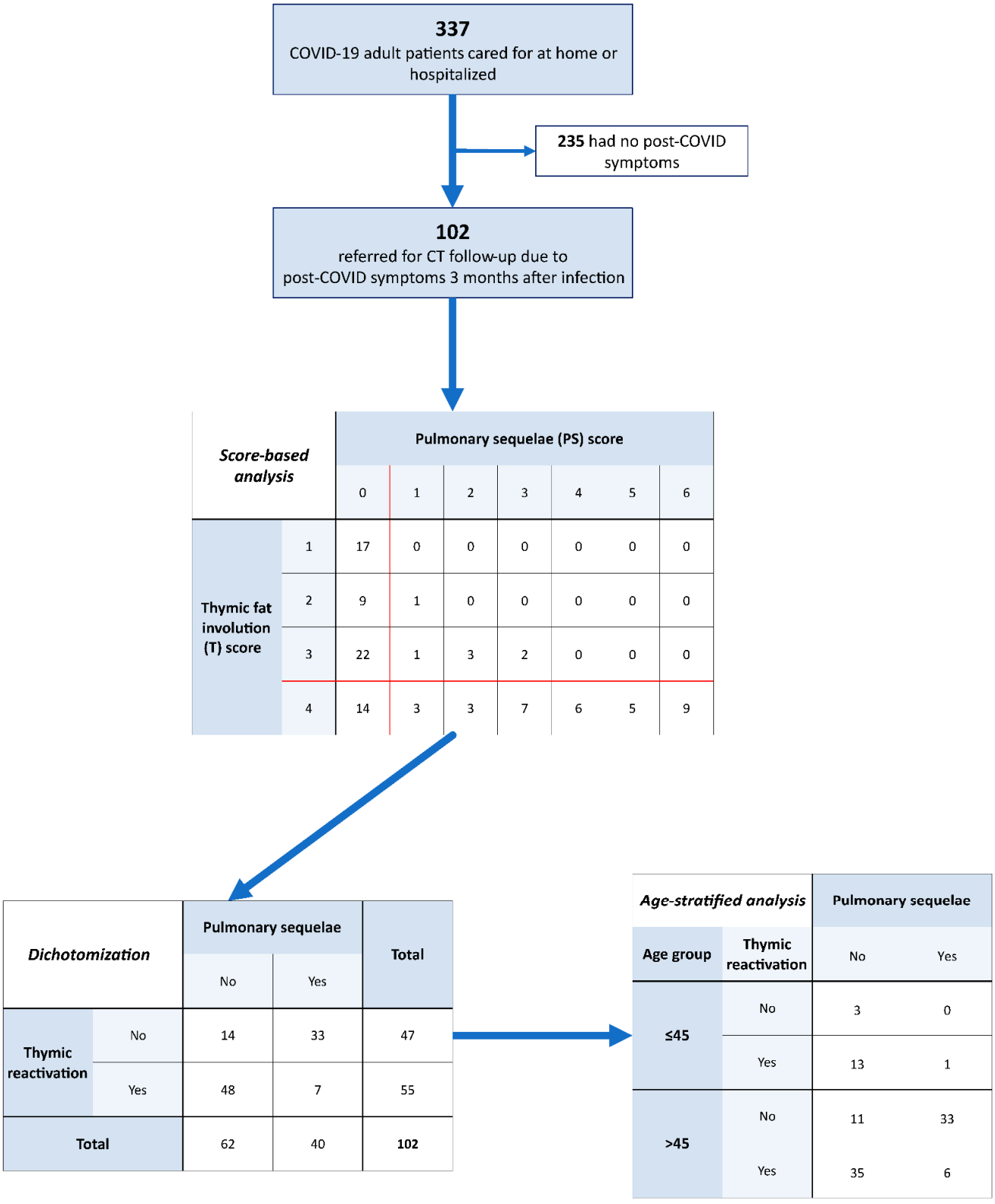


Figure 3. Partial fatty involution of the thymus, visible in the mediastinal window (**a**), associated with mild parenchymal abnormalities graded as pulmonary sequelae score 2, in parenchymal reconstructions (panels **b**,**c**).

3. Results

As shown in the study flowchart (Figure 4), 235 out of 337 COVID-19 patients had a complete remission of symptoms, while the remaining 102 patients underwent CT follow-up for post-COVID respiratory symptoms at a mean 2.5 ± 0.5 months after hospital discharge, constituting the study population (37/102 females, 36%; median age 58 years, interquartile range 50–63 years). Among these 102 patients, 40 (39%) were from Center 1 (13/40 females, 33%; median age 58 years, interquartile range 52–65 years) and 62 (61%) from Center 2 (25/62 females, 40%; median age 57 years, interquartile range 48–63 years).

The inter-reader agreement was almost perfect both for the evaluation of pulmonary sequelae ($\kappa = 0.920$) and of thymic fat infiltration ($\kappa = 0.910$). The thymus was detectable in 55/102 patients (54%), and all 17 patients with a T score of 1 (well-recognizable thymus characterized by predominantly soft-tissue attenuation, similar to the muscle density) had a pulmonary sequelae score of 0 (absent or minimal pulmonary parenchymal changes). Pulmonary sequelae (pulmonary sequelae score 1 to 6) were instead detected in 40/102 patients (39%) and were significantly more frequent in the group of patients without thymic reactivation (T score 4, 33/47, 70%) than in the group of patients with progressively more evident signs of thymus hyperplasia (T score 1–3, 7/55, 13%, $p < 0.001$), this difference being confirmed in the age-stratified analysis with a 45-year age cut-off (Cochran–Mantel–Haenszel test $p < 0.001$). At multivariable regression analysis (Table 1), thymic involution showed the strongest association with pulmonary sequelae presence (OR 9.3, 95% CI 3.0–28.2, $p < 0.001$), followed by age expressed as a continuous variable (OR 1.1 for each year, 95% CI 1.0–1.2, $p = 0.007$) (Figure 5).



Score-based analysis		Pulmonary sequelae (PS) score						
		0	1	2	3	4	5	6
Thymic fat involution (T) score	1	17	0	0	0	0	0	0
	2	9	1	0	0	0	0	0
	3	22	1	3	2	0	0	0
	4	14	3	3	7	6	5	9

Dichotomization		Pulmonary sequelae		Total
		No	Yes	
Thymic reactivation	No	14	33	47
	Yes	48	7	55
Total		62	40	**102**

Age-stratified analysis		Pulmonary sequelae	
Age group	Thymic reactivation	No	Yes
≤45	No	3	0
	Yes	13	1
>45	No	11	33
	Yes	35	6

Figure 4. Study flowchart. Red lines represent dichotomization thresholds.

Table 1. Presence of pulmonary sequelae: univariate and multivariable regression analysis.

Variable	Group	Univariate Regression Analysis Odds Ratio (95% CI)	*p*	Multivariable Regression Analysis Odds Ratio (95% CI)	*p*
Age *	–	1.13 (1.07–1.19)	<0.001	1.09 (1.02–1.17)	0.007
Sex	Females	1 (reference category)	–	1 (reference category)	–
	Males	3.52 (1.40–8.83)	0.007	1.65 (0.50–5.37)	0.41
Thymic fat involution	No	1 (reference category)	–	1 (reference category)	–
	Yes	16.16 (5.89–44.37)	<0.001	9.25 (3.03–28.21)	<0.001

* Continuous variable in 1-year units.

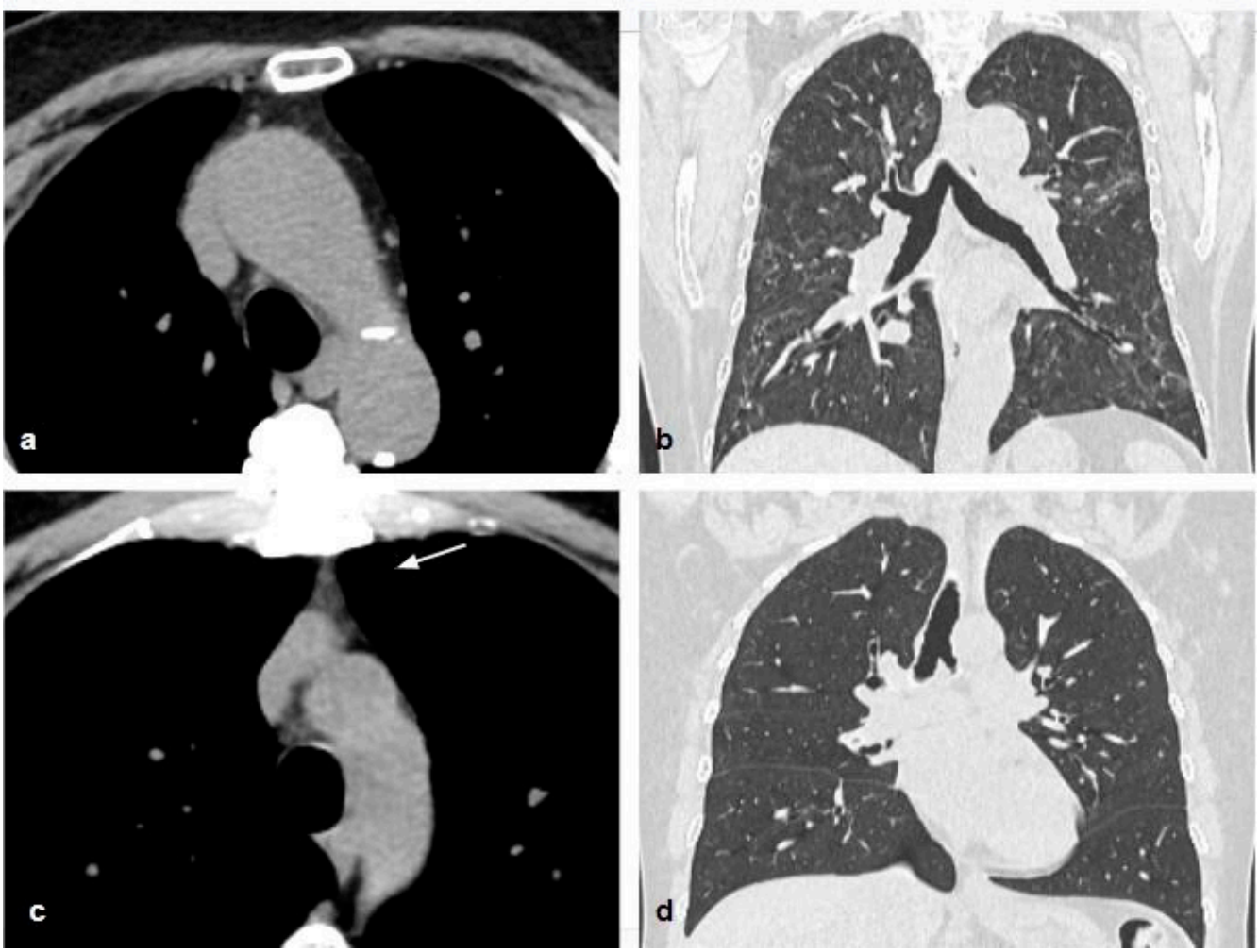


Figure 5. Follow-up unenhanced chest CT images of a 64-year-old (panels **a**,**b**) and a 65-year-old (panels **c**,**d**) male patient. The first patient had a complete fat involution of the thymus on the mediastinal window (**a**); coronal multiplanar reconstruction with lung parenchymal window shows bilateral persistence of ground-glass opacities involving <50% of pulmonary parenchyma (**b**). The second patient showed a well-identifiable thymus with partial fat involution (**c**), without any sign of parenchymal sequelae (**d**).

4. Discussion

This study investigated the hypothesis that the thymus—a critical organ in the immune system—may play a pivotal role in the outcomes of SARS-CoV-2 infection, focusing on the thymic appearance during CT in patients who had previously been hospitalized for COVID-19, without the need for invasive ventilatory support, and who underwent a follow-up chest CT three months after discharge. The central findings of the study suggest a strong association between the enhanced visibility of the thymus in CT scans and the absence of pulmonary sequelae at follow-up, supporting the hypothesis that thymic hyperplasia (or the absence of thymic involution) may act protectively against adverse COVID-19 outcomes, especially lung alterations.

As individuals recover from the acute phase of SARS-CoV-2 infection, some face persistent respiratory challenges that extend beyond the initial recovery period. The long-term pulmonary sequelae of COVID-19 have emerged as a substantial concern, with a notable focus on the development of pulmonary fibrosis, a chronic progressive and mostly fatal disease characterized by interstitial collagen deposition with varying degrees of alveolar bronchiolization [18]. Although the vast majority of patients do not experience the most severe form of pulmonary fibrosis, many do experience long-term consequences.

COVID-19 acute and chronic manifestations are detectable through CT scans [19–23], the reference imaging method to reveal the presence of irregular tissue patterns and areas of increased density [18]. Ground-glass opacities, fibrotic changes, and vascular abnormalities are among the notable findings in individuals who have recovered from the acute phase of infection [19]. These residual changes are indicative of the virus's ability to induce lung inflammation and injury, resulting in long-lasting structural alterations. As fibrosis can impair the normal functioning of the respiratory system, this leads to reduced lung compliance and—depending on the extension—compromised gas exchange.

The mechanisms by which COVID-19 induces pulmonary fibrosis are complex and multifaceted [24]. The virus can trigger a dysfunctional immune response, leading to persistent inflammation and the activation of fibroblasts, cells responsible for collagen production. The thymus is the main anatomical site for the production and education of T cells and is a key organ in the immune system, where it plays an important role in the protection from pathogens early in life. However, the thymus physiologically undergoes progressive involution with age, resulting in reduced production of naïve T cells and increased susceptibility to infections [25].

Some authors have speculated that thymic changes play a role in determining the prognosis of COVID-19 patients [12,14]. In a study by Palmer et al. [12], COVID-19 hospitalization rates rose exponentially with age, inversely proportional to thymic T cell production, suggesting that thymic involution is an important factor in the decline of the immune system and may also be an important clue in understanding disease progression, and highlighting the role of the T cell mediated immune response as a crucial determinant in COVID-19 outcomes. In an acute care setting, Cuvelier et al. [14] reported that in COVID-19 patients, thymus enlargement was associated with increased T lymphocyte production, which appeared to be a beneficial adaptation to virus-induced lymphopenia, and that the lack of thymic activity and reactivation in older COVID-19 patients could contribute to a worse prognosis. Furthermore, the rebooting of T cell activity by enhancing thymic function and improving immune cell-induced cytokine storm has been suggested as a potential treatment to improve antiviral immunity and COVID-19 outcomes [26].

Despite this evidence, to the best of our knowledge, the relationship between the thymus and long-term post-COVID-19 pulmonary sequelae had yet to be investigated. In our study, the detection of the thymus in CT scans was associated with a significantly lower incidence of pulmonary sequelae, and logistic regression analysis indicated that thymic involution is strongly linked to the presence of pulmonary sequelae, with a notably high odds ratio. These findings were further substantiated by age-stratified analysis, where a surprisingly high rate of patients above age 45 had thymic visibility (48%), with a significantly lower proportion of pulmonary sequelae (15%) compared to patients with typical

thymic involution (75%), underscoring the potential significance of thymic hyperplasia as a protective factor not only in the acute setting but also against long-term respiratory complications in COVID-19 survivors.

The main limitations of this study are its retrospective nature, the relatively small sample size, and the lack of CT examinations performed before SARS-CoV-2 infection, which does not allow to determine whether the thymic hyperplasia was a reactive condition or a pre-existing state of increased T cell-mediated response in a subset of patients. Another intrinsic limitation lies in the fact that unenhanced chest CT does not provide high-level functional information, such as that which could be gathered from 18F-FDG-PET/CT, which is increasingly being used to evaluate and characterize viral and inflammatory lung diseases [27]. Indeed, inflammatory reactions that cause acute lung injury in the context of viral pneumonia are triggered by the chemokine recruitment of neutrophils, monocytes, and effector T cells, whose activity relies heavily on anaerobic glycolysis and glucose intake from the environment, resulting in 18F-FDG-avid foci. PET/CT can identify increased thymic metabolic activity in response to SARS-CoV-2 infection, as highlighted in patients who received a COVID-19 vaccine [28], corresponding to thymic activation that may be present also during COVID-19, when an effective immune response occurs.

5. Conclusions

This study contributes to the ongoing exploration of factors influencing the long-term consequences of COVID-19, prompting further research into the dynamics of thymic function during and after viral infections. Our findings support the role of thymus activity as a predictor of long-term patients' pulmonary outcomes and as a protective factor against fibrosis after COVID-19. If validated through additional studies conducting a systematic evaluation of the thymic area with appropriate CT settings during both hospitalization and follow-up—along with laboratory findings—these data could inform clinical practice, especially in identifying individuals at higher risk for post-COVID-19 pulmonary complications.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of Interest: Author Marco Alì was employed by the company Bracco Imaging SpA. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Antonio, G.E.; Wong, K.T.; Hui, D.S.C.; Wu, A.; Lee, N.; Yuen, E.H.Y.; Leung, C.B.; Rainer, T.H.; Cameron, P.; Chung, S.S.C.; et al. Thin-Section CT in Patients with Severe Acute Respiratory Syndrome Following Hospital Discharge: Preliminary Experience. *Radiology* **2003**, *228*, 810–815. [CrossRef] [PubMed]
2. Ooi, G.C.; Khong, P.L.; Müller, N.L.; Yiu, W.C.; Zhou, L.J.; Ho, J.C.M.; Lam, B.; Nicolaou, S.; Tsang, K.W.T. Severe Acute Respiratory Syndrome: Temporal Lung Changes at Thin-Section CT in 30 Patients. *Radiology* **2004**, *230*, 836–844. [CrossRef] [PubMed]

3. Das, K.M.; Lee, E.Y.; Singh, R.; Enani, M.A.; Al Dossari, K.; Van Gorkom, K.; Larsson, S.G.; Langer, R.D. Follow-up chest radiographic findings in patients with MERS-CoV after recovery. *Indian J. Radiol. Imaging* **2017**, *27*, 342–349. [CrossRef] [PubMed]
4. George, P.M.; Wells, A.U.; Jenkins, R.G. Pulmonary fibrosis and COVID-19: The potential role for antifibrotic therapy. *Lancet Respir. Med.* **2020**, *8*, 807–815. [CrossRef]
5. Murphy, M.C.; Little, B.P. Chronic Pulmonary Manifestations of COVID-19 Infection: Imaging Evaluation. *Radiology* **2023**, *307*, e222379. [CrossRef] [PubMed]
6. Xie, Y.; Bowe, B.; Al-Aly, Z. Burdens of post-acute sequelae of COVID-19 by severity of acute infection, demographics and health status. *Nat. Commun.* **2021**, *12*, 6571. [CrossRef] [PubMed]
7. Havervall, S.; Rosell, A.; Phillipson, M.; Mangsbo, S.M.; Nilsson, P.; Hober, S.; Thålin, C. Symptoms and Functional Impairment Assessed 8 Months After Mild COVID-19 Among Health Care Workers. *JAMA* **2021**, *325*, 2015–2016. [CrossRef]
8. Evans, R.A.; Leavy, O.C.; Richardson, M.; Elneima, O.; McAuley, H.J.C.; Shikotra, A.; Singapuri, A.; Sereno, M.; Saunders, R.M.; Harris, V.C.; et al. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: A prospective observational study. *Lancet Respir. Med.* **2022**, *10*, 761–775. [CrossRef] [PubMed]
9. Whitaker, M.; Elliott, J.; Chadeau-Hyam, M.; Riley, S.; Darzi, A.; Cooke, G.; Ward, H.; Elliott, P. Persistent COVID-19 symptoms in a community study of 606,434 people in England. *Nat. Commun.* **2022**, *13*, 1957. [CrossRef]
10. Subramanian, A.; Nirantharakumar, K.; Hughes, S.; Myles, P.; Williams, T.; Gokhale, K.M.; Taverner, T.; Chandan, J.S.; Brown, K.; Simms-Williams, N.; et al. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nat. Med.* **2022**, *28*, 1706–1714. [CrossRef]
11. Kellogg, C.; Equils, O. The role of the thymus in COVID-19 disease severity: Implications for antibody treatment and immunization. *Hum. Vaccin. Immunother.* **2021**, *17*, 638–643. [CrossRef] [PubMed]
12. Palmer, S.; Cunniffe, N.; Donnelly, R. COVID-19 hospitalization rates rise exponentially with age, inversely proportional to thymic T-cell production. *J. R. Soc. Interface* **2021**, *18*, rsif.2020.0982. [CrossRef] [PubMed]
13. Poulin, J.-F.; Viswanathan, M.N.; Harris, J.M.; Komanduri, K.V.; Wieder, E.; Ringuette, N.; Jenkins, M.; McCune, J.M.; Sékaly, R.-P. Direct Evidence for Thymic Function in Adult Humans. *J. Exp. Med.* **1999**, *190*, 479–486. [CrossRef] [PubMed]
14. Cuvelier, P.; Roux, H.; Couëdel-Courteille, A.; Dutrieux, J.; Naudin, C.; Charmeteau de Muylder, B.; Cheynier, R.; Squara, P.; Marullo, S. Protective reactive thymus hyperplasia in COVID-19 acute respiratory distress syndrome. *Crit. Care* **2021**, *25*, 4. [CrossRef] [PubMed]
15. Çakmak, V.; Yılmaz, A.; Sarı, T.; Çakmak, P.; Özen, M.; Herek, D.; Oskay, A.; Yilmaz, A.; Sari, T.; Çakmak, P.; et al. Evaluation of the chest computed tomography and hemogram data in patients with COVID-19: The importance of thymus. *Turk. J. Med. Sci.* **2021**, *51*, 991–1000. [CrossRef] [PubMed]
16. Landis, J.R.; Koch, G.G. The Measurement of Observer Agreement for Categorical Data. *Biometrics* **1977**, *33*, 159–174. [CrossRef] [PubMed]
17. Ackman, J.B.; Kovacina, B.; Carter, B.W.; Wu, C.C.; Sharma, A.; Shepard, J.-A.O.; Halpern, E.F. Sex Difference in Normal Thymic Appearance in Adults 20–30 Years of Age. *Radiology* **2013**, *268*, 245–253. [CrossRef] [PubMed]
18. Liao, X.; Li, D.; Liu, Z.; Ma, Z.; Zhang, L.; Dong, J.; Shi, Y.; Gu, X.; Zheng, G.; Huang, L.; et al. Pulmonary Sequelae in Patients After Recovery From Coronavirus Disease 2019: A Follow-Up Study With Chest CT. *Front. Med.* **2022**, *8*, 686878. [CrossRef]
19. Cellina, M.; Orsi, M.; Valenti Pittino, C.; Toluian, T.; Oliva, G. Chest computed tomography findings of COVID-19 pneumonia: Pictorial essay with literature review. *Jpn. J. Radiol.* **2020**, *38*, 1012–1019. [CrossRef]
20. Sardanelli, F.; Cozzi, A.; Monfardini, L.; Bnà, C.; Foà, R.A.; Spinazzola, A.; Tresoldi, S.; Cariati, M.; Secchi, F.; Schiaffino, S. Association of mediastinal lymphadenopathy with COVID-19 prognosis. *Lancet Infect. Dis.* **2020**, *20*, 1230–1231. [CrossRef]
21. Monfardini, L.; Morassi, M.; Botti, P.; Stellini, R.; Bettari, L.; Pezzotti, S.; Alì, M.; Monaco, C.G.; Magni, V.; Cozzi, A.; et al. Pulmonary thromboembolism in hospitalised COVID-19 patients at moderate to high risk by Wells score: A report from Lombardy, Italy. *Br. J. Radiol.* **2020**, *93*, 20200407. [CrossRef] [PubMed]
22. Spagnolo, P.; Cozzi, A.; Foà, R.A.; Spinazzola, A.; Monfardini, L.; Bnà, C.; Alì, M.; Schiaffino, S.; Sardanelli, F. CT-derived pulmonary vascular metrics and clinical outcome in COVID-19 patients. *Quant. Imaging Med. Surg.* **2020**, *10*, 1325–1333. [CrossRef] [PubMed]
23. Schiaffino, S.; Codari, M.; Cozzi, A.; Albano, D.; Alì, M.; Arioli, R.; Avola, E.; Bnà, C.; Cariati, M.; Carriero, S.; et al. Machine Learning to Predict In-Hospital Mortality in COVID-19 Patients Using Computed Tomography-Derived Pulmonary and Vascular Features. *J. Pers. Med.* **2021**, *11*, 501. [CrossRef]
24. Alrajhi, N.N. Post-COVID-19 pulmonary fibrosis: An ongoing concern. *Ann. Thorac. Med.* **2023**, *18*, 173–181. [CrossRef] [PubMed]
25. Thapa, P.; Farber, D.L. The Role of the Thymus in the Immune Response. *Thorac. Surg. Clin.* **2019**, *29*, 123–131. [CrossRef] [PubMed]
26. Wang, W.; Thomas, R.; Oh, J.; Su, D.-M. Thymic Aging May Be Associated with COVID-19 Pathophysiology in the Elderly. *Cells* **2021**, *10*, 628. [CrossRef]

27. Katal, S.; Amini, H.; Gholamrezanezhad, A. PET in the diagnostic management of infectious/inflammatory pulmonary pathologies: A revisit in the era of COVID-19. *Nucl. Med. Commun.* **2021**, *42*, 3–8. [CrossRef]
28. Luthria, G.; Baratto, L.; Adams, L.; Morakote, W.; Daldrup-Link, H.E. Increased Metabolic Activity of the Thymus and Lymph Nodes in Pediatric Oncology Patients After Coronavirus Disease 2019 Vaccination. *J. Nucl. Med.* **2024**, *65*, 22–24. [CrossRef]