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Impact of Thymic Response in COVID-19 Pneumonia on Disease Severity and Mortality-As Assessed on CT-Chest

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ABSTRACT

Objective: To determine the effect of thymic response to COVID-19 pneumonia on imaging and its impact on disease severity and outcome.

Study Design: Cross-sectional study.

Place and Duration of Study: Armed Forces Institute of Radiology and Imaging (AFIRI), Rawalpindi Pakistan, from Mar to Jul 2020.

Methodology: A total of 1620 COVID-19 patients above the age of 18, of either gender, were included in the study. Their findings on High-Resolution CT (HRCT) chest were recorded and graded according to the CT severity score (CTSS) out of a total of 40; less than or equal to 19 was taken as mild while >20 scores were considered as severe disease. The thymic response was assessed by imaging appearance on CT and was graded from 0-3 as follows: fatty, predominantly fatty, mixed density (fat and soft density), and soft density. Fatty replacement implied thymic involution, while soft density depicted a reactivation of thymic tissue after a disease process depictive adequate thymic response.

Results: A significant difference in thymic response was observed in patients of different age groups (p<0.001), with the younger age group demonstrating thymic reactivation/ response in the majority (170/244, 69.7%). CT severity score and mortality were significantly higher in older patients demonstrating poor thymic response to COVID pneumonia.

Conclusion: Response of the thymus to acute viral infection by Sars COVID-19 is impaired as age progresses; this accounts for greater disease severity, morbidity and mortality in older patients.

Keywords: COVID pneumonia, Thymus, Reactivation, Response.

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INTRODUCTION

Thymus is a lymphatic organ located in the anterior mediastinum; it is pivotal in providing immunity against diseases. It regulates immune response through T cells and enhancement of humoral immunity through B cells.[1] There is a gradual replacement of thymic tissue as age progresses, with fat replacing the parenchyma of the normal thymus. Relative sparing in females is postulated to be due to encoding an extra X chromosome of proteins that regulate the thymic response of the immune system.[2] Since many factors also affect the prognosis of COVID-19 patients, this highlights the importance of thymic reactivation in COVID-19 pneumonia.[3] The decreased thymic function represents a reduced number and activity of T cells, resulting in a poor immune response to viral infections and cancer. This was postulated as one possible reason children fared better than adults in the pandemic.[4,5]

CT remains the first choice of investigation for evaluating the thymus due to soft tissue contrast with the mediastinal fat.[6] However, the increasing role of Magnetic Resonance Imaging (MRI) is also being established in its radiological assessment. This study assessed thymus response according to its appearance on CT and its relation to the severity of the disease process and mortality in COVID pneumonia. Age-related involutory changes may explain the poor response and increased mortality in the older age group the latter acting as an independent prognostic factor.[7]

The severity of pneumonia was assessed according to the CT Severity Score (CTSS), which correlates well with the patients' clinical outcome and hospital stay.[8,9] CTSS was calculated by determining the degree of involved lung segments individually-scored as one if segmental involvement is less than 50% or two if it is greater than 50%. The maximum score assigned on either side (10 segments each) was 20 for each lung. Hence the scoring was done out of a total score of 40, with a cut-off between mild and severe disease being 20.[10] In addition, the study evaluated thymic response to COVID-19 pneumonia

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across age groups and its relation to disease severity and mortality.

METHODOLOGY

The cross-sectional study was conducted at the Armed Forces Institute of Radiology and Imaging, (AFIRI) Rawalpindi Pakistan, from March to July 2020, fea-turing all RT PCR positive patients of COVID pneumonia coming to CT department for High-Resolution CT (HRCT) chest (n=1620). Approval for the study was taken by Institutional Ethical Review Board (Certificate No: 0078). The sample size calculated keeping the COVID-positive population of Punjab as per the official figures of the Pakistan Government at the time of the study.[11]

Inclusion Criteria: Rt PCR-positive COVID patients aged above 18 years, of either gender, were included in the study.

Exclusion Criteria: Those patients who were clinically suspected of having COVID pneumonia were excluded from the study.

Age, gender and radiological findings of COVID pneumonia were recorded. CT was studied for disease severity (on lung window) as per CT severity score (CTSS). Thymus density was graded (on the mediastinal window) into four groups: Grade-0: fatty; 1: predominantly fatty; 2: mixed fat and soft tissue; and Grade-3: soft tissue density.[12] The fat density of the thymus represented no/minimal thymic response to disease, while soft density represented a good response. Thymus scoring was correlated with the severity of COVID pneumonia in lungs and disease outcome; the association of this relationship with demographics (age and gender) was also inferred. Thymic scoring of patients was performed on the mediastinal window of the Chest, while CTSS scoring was performed on the lung window. Findings were read by three consultant Radiologists having more than 10 years of experience.

Data were analyzed using Statistical Package for the social sciences (SPSS) version 23.00 and MS Excel 2016 software. Mean±SD were calculated for continuous variables. Frequency and percentage were calculated for categorical variables. The chi-square test and t-test were used. The p-value ≤ 0.05 was considered significant.

RESULTS

The study included 1620 patients, out of which 346(21.4%) were females and 1274(78.6%) were males. A significant difference in thymic response was observed in patients of different age groups (p<0.001), with the youngest age group (19-30 years) demonstrating thymic reactivation/ response in the majority, at n= 170/244(69.7%). In comparison, only n=9/352 (2.6%) of patients older than 61 years demonstrated good thymic response. A significant association was also found between the severity of the CTSS scores and thymic response (p<0.001) with the greater number of patients with a mild CTSS (320/1214, 26.4%) having a soft density thymus, as compared to only (10/406, 2.5%) patients with a severe CTSS. Mortality was higher (31/40(3.9%) in patients having a poor thymic response (Table).

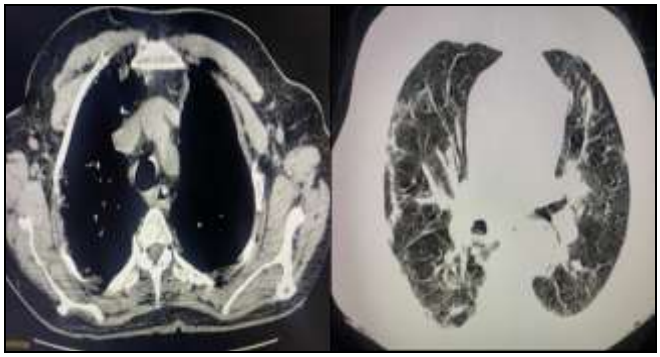
Table: Imaging response of Thymus in COVID Pneumonia and its relation to Patients' Age, Disease Severity and Mortality (n=1620)

Variables	Grade-0 (fatty) n(%)	Grade-I (Predominantly Fatty) n(%)	Grade-II (Mixed Density) n(%)	Grade-III (Soft Density) n(%)	p-value
Age					
19-30 years	18(2.3)	12(4.6)	44(18.9)	170(51.5)	<0.001
31-45 years	163(20.5)	93(35.5)	96(41.2)	127(38.5)	
46-60 years	338(42.5)	96(41.2)	75(32.2)	24(7.3)	
>61 years	276(34.7)	49(18.7)	18(7.7)	9(2.7)	
CTSS					
Mild	468(58.9)	214(81.7)	212(91)	320(97)	<0.001
Severe	327(41.1)	48(18.3)	21(9)	10(3)	
Mortality					
Survived	764(96.1)	259(98.9)	228(97.9)	329(99.7)	0.002
Expired	31(3.9)	3(1.1)	5(2.1)	1(0.3)	

DISCUSSION

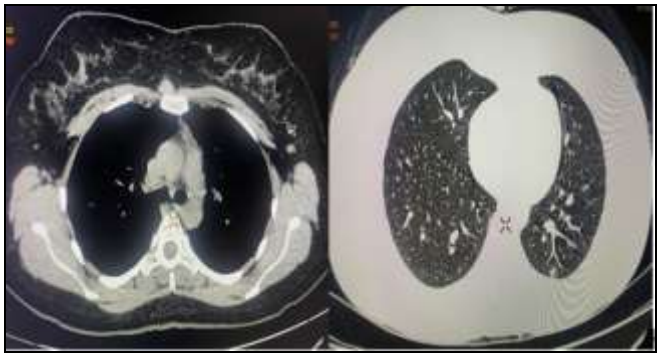
Age-related involutory changes reduce the size of the thymus with replacement of normal parenchyma with fat as seen on CT Chest; hence age plays an important part in an individual's response to disease. Younger patients in our study fared better than the

older population in response to COVID pneumonia, both in severity and mortality (Figures-1 and 2). This fact is also supported by researchers who studied the dynamics behind the difference between the adult and paediatric response to COVID-19 pneumonia world-wide, considering age-related thymic-mediated immune response as a major factor.[12,13] Another study has compared the mortality rates across different age groups, from nil to a minimum of 1-19 years.[14]



(a) (b)

Figure-1: Thymic Score of 0 (Fat Replacement of Thymus in Anterior Mediastinum) in a 56-year-old patient of COVID Pneumonia (CTSS 18/40) -(a) Mediastinal Window (b) Lung Window



(a) (b)

Figure-2: Thymic Score of 3 (Soft Density Thymus in Anterior Mediastinum) in a 29-year-old female with COVID Pneumonia (CTSS 2/40)- (a) Mediastinal Window (b) Lung Window

In healthy patients, females were found to have delayed involution of thymic tissue compared to males in the younger age group (20-30 years), although this was not consistent through all age groups.[15] Our study revealed no significant difference between gender as per imaging criteria, while age remained one of the significant differentiating features in thymic response. A study conducted on intensive care patients of COVID found that patients suffering from advanced pneumonia developed radiological enlargement of the thymus representing its reactivation with subsequent better prognosis and disease progression.[16] In our patients, we found that the greater the age and severity of the disease, the lesser the thymic response and hence the higher mortality (Figure-3). Patients with raised Interleukin (IL-6) and C-Reactive Proteins (CRP) were found to have poor thymic function supporting our findings since these inflammatory markers are elevated in COVID pneumonia.[17] Since a dysfunctional thymus associated with a reduction in protective effect is postulated to be an aggravating factor in chronic and acute infective diseases in the elderly, research is in progress to rejuvenate age-related thymic immune response as a defence against COVID with an attempt to enhance the response of the elderly to COVID vaccination. No direct effect of SARS COV-19 virus on thymic tissue, including the thymocytes or thymic epithelial cells, has been reported so far.[18]

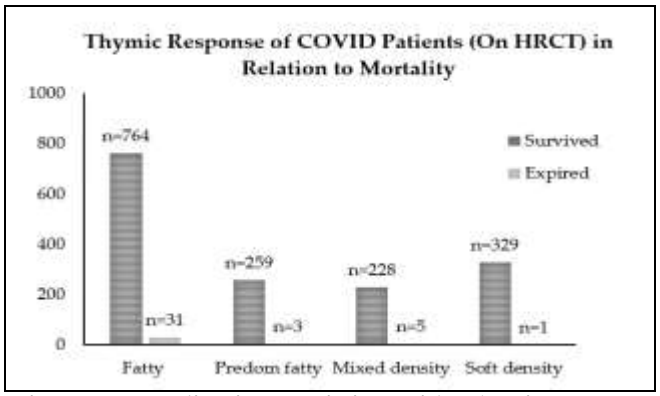


Figure-3: Mortality in association with Thymic Response imaging pattern: Majority of expired Patients showing Fatty Replacement of Thymus Tissue -Grade

This study describes the radiological response of the thymus inferring its functionality, in a large group of adult COVID patients (n=1620). The limitation of this study was that quantification of thymic function was not done through blood samples; the thymic response was assessed solely upon radiological scoring of the thymus on the CT chest.

CONCLUSION

Thymic response, as depicted by the radiological appearance on the CT chest, is poor in elderly patients compared to younger patients of COVID pneumonia, with the resultant increase in severity of the disease and mortality in this age group.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SIZ: Study design, drafting the manuscript, data interpretation, , approval of the final version to be published.

HN & ARS: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

NZ & AS: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Nasseri F, Eftekhari F. Clinical and radiologic review of the normal and abnormal thymus: pearls and pitfalls. Radiographics 2010; 30(2): 413-428. doi: 10.1148/rg.302095131.
2. 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(3): 638-643. doi: 10.1080/21645515.2020.1818519.
3. Yang H, Youm YH, Vandanmagsar B, Rood J, Kumar KG, Butler AA, *et al*. Obesity accelerates thymic aging. Blood 2009; 114(18): 3803-3812. doi: 10.1182/blood-2009-03-213595.
4. Zeyrek D, Ozturk E, Ozturk A, Cakmak A. Decreased thymus size in full-term newborn infants of smoking mothers. Med Sci Monit 2008; 14(8): CR423-426.
5. Güneş H, Dinçer S, Acıpayam C, Yurttutan S, Özkars MY. What chances do children have against COVID-19? Is the answer hidden within the thymus? Eur J Pediatr 2021; 180(3): 983-986.
6. Hussain AM, Packota G, Major PW. Role of different imaging modalities in assessment of temporoman-dibular joint erosions and osteophytes: a systematic review. Dentomaxillofac Radiol 2008; 37(2): 63-71. doi: 10.1259/dmfr/ 16932758.
7. Araki T, Nishino M, Gao W, Dupuis J, Murakami T, *et al*. Normal thymus in adults: appearance on CT and associations with age, sex, BMI and smoking. Eur Radiol 2016; 26(1): 15-24.
8. 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(3): 638-643.
9. Saeed GA, Gaba W, Shah A, Al Helali AA, Raidullah E, Al Ali AB, et al. Correlation between Chest CT Severity Scores and the Clinical Parameters of Adult Patients with COVID-19 Pneumonia. Radiol Res Pract 2021; 2021: 6697677. doi: 10.1155/2021/66/97677.
10. Raoufi M, Safavi Naini SAA, Azizan Z, Jafar Zade F, Shojaeian F, Ghanbari Boroujeni M. Correlation between Chest Computed Tomography Scan Findings and Mortality of COVID-19 Cases; a Cross sectional Study. Arch Acad Emerg Med 2020; 8(1): e57.
11. Lins MP, Smaniotto S. Potential impact of SARS-CoV-2 infection on the thymus. Can J Microbiol 2021; 67(1): 23-28. doi: 10.1139/cjm-2020-0170.
12. Fialkowski A, Gernez Y, Arya P, Weinacht KG, Kinane TB, Yonker LM. Insight into the pediatric and adult dichotomy of COVID-19: Age-related differences in the immune response to SARS-CoV-2 infection. Pediatr Pulmonol 2020; 55(10): 2556-2564. doi: 10.1002/ppul.24981.
13. Rehman S, Majeed T, Ansari MA, Ali U, Sabit H, Al-Suhaimi EA. Current scenario of COVID-19 in pediatric age group and physiology of immune and thymus response. Saudi J Biol Sci 2020; 27(10): 2567-2573. doi: 10.1016/j.sjbs.2020.05.024.
14. Ackman JB, Kovacina B, Carter BW, Wu CC, Sharma A, Shepard JA, et al. Sex difference in normal thymic appearance in adults 20-30 years of age. Radiology 2013; 268(1): 245-53. doi: 10.1148/radiol.13121104.
15. Feinstein L, Ferrando-Martínez S, Leal M, Zhou X, Sempowski GD, Wildman DE, Uddin M, et al. Population Distributions of Thymic Function in Adults: Variation by Sociodemographic Characteristics and Health Status. Biodemography Soc Biol 2016; 62(2): 208-221. doi: 10.1080/19485565.2016.1172199.
16. Cuvelier P, Roux H, Couëdel-Courteille A, Dutrieux J, Naudin C, Charmeteau de Muylder B, et al. Protective reactive thymus hyperplasia in COVID-19 acute respiratory distress syndrome. Crit Care 2021; 25(1): 4. doi: 10.1186/s13054-020-03440-1.
17. Gruver AL, Sempowski GD. Cytokines, leptin, and stress-induced thymic atrophy. J Leukoc Biol 2008; 84(4): 915-923. doi: 10.1189/jlb.0108025.
18. Wang W, Thomas R, Oh J, Su DM. Thymic Aging May Be Associated with COVID-19 Pathophysiology in the Elderly. Cells 2021; 10(3): 628. doi: 10.3390/cells10030628.