HUE UNIVERSITY
UNIVERSITY OF MEDICINE AND PHARMACY

DUONG MINH TRI

STUDY OF CLINICAL, SUBCLINICAL CHARACTERISTICS AND RS35705950 VARIANTS OF THE MUC5B GENE IN PATIENTS RHEUMATOID ARTHRITIS WITH INTERSTITIAL LUNG DISEASE

SUMMARY DOCTOR OF MEDICINE THESIS

Field: INTERNAL MEDICINE
Code: 9720107

HUE, 2026

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Science Instructor:

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2. Dr. TRINH HOANG KIM TU

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ASK THE PROBLEM

Rheumatoid arthritis (Rheumatoid arthritis) is a chronic inflammatory joint disease of an autoimmune nature, the most common among joint diseases. This is a common disease in Vietnam as well as many other countries around the world. The incidence is about 0.5-1% of the population of some European countries and about 0.17-0.3% in Asian countries. The most basic and earliest lesion of the disease is synovitis of many joints, which usually manifests itself in small and medium joints.

Among the key findings, the segment gene variant *MUC5B* were found to have a clearer association with interstitial pulmonary disease in patients with RA, particularly in the European population. Patients with RA carry fragmented gene variants *MUC5B* will have a 3.1-fold increased risk of interstitial lung disease and a 6.1-fold increased risk of interstitial pneumonia detected on a high-resolution CT scan.

In Vietnam, the treatment of RA is still a challenge in clinical practice. In addition, the detection, treatment and management of interstitial pulmonary disease in patients with RA is still controversial among clinicians. Studies reporting on the clinical, risk factors and treatment for interstitial pulmonary disease on RA are still very few. In the southern region, there have been no reports on this issue and especially research on gene variants. Therefore, we conducted this study with the research question: ***So what is the ratio of MUC5B gene variants, clinical and subclinical characteristics of interstitial pulmonary disease to RA?***. From there, we came up with the following research objectives:

1. Determination of ILD rate, clinical and subclinical characteristics and description of the rs35705950 variant of the MUC5B gene in patients with ILD.

2. Evaluation of the association between clinical, subclinical, rs35705950 variant of MUC5B gene, disease activity and 4 ILD phenotypes.

Chapter 1
DOCUMENT OVERVIEW

1.3. RISK FACTORS FOR THE DEVELOPMENT OF INTERSTITIAL LUNG DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS

There are many factors associated with interstitial pneumonia in patients with rheumatoid arthritis: age, gender, smoking, high concentration of anti-CCP, serum RF, disease activity level.

1.3.1. Age

1.3.2. Gender

1.3.3. Smoking

1.3.4. RF and anticyclic citrullinated protein antibodies (ACPAs)

1.3.5. Genetic factors - *MUC5B*

Research by Juge P.A. found that there is a common genetic background between common interstitial pneumonia in rheumatoid arthritis patients and idiopathic pulmonary fibrosis including RS35705950, a promoter variant *MUC5B*, representing the main genetic risk factor in both diseases. The study found that the promoter variant *MUC5B* is associated with an increased risk of interstitial lung disease in patients with rheumatoid arthritis. *MUC5B* encoding a protein mucin plays an essential role in mucus secretion in many organs, including the lungs. However, its exact pathogenic mechanism has not been clearly described. Interstitial pulmonary disease associated with rheumatoid arthritis has some characteristics in common with idiopathic pulmonary fibrosis, including the same environmental risk factors, high prevalence of the common interstitial pneumonia phenotype, advanced pulmonary fibrosis, and poor survival. An exome sequencing study found that patients with rheumatoid arthritis associated with interstitial lung disease had an excess of variants in genes previously associated with familial interstitial pneumonia, including *TERT, RTEL1, PARN, and SFTPC*. Genotype Determination of Mononucleotide Polymorphism *MUC5B* rs35705950 use by qPCR quantitative polymerase chain reaction assay.

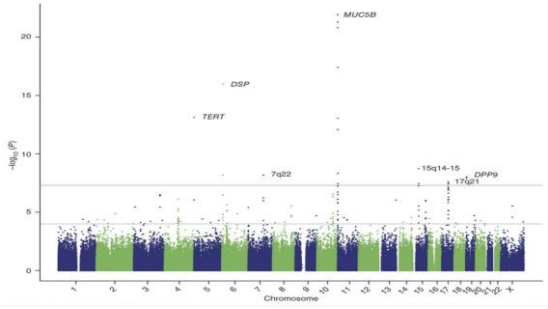

Figure 1.5: Genes associated with interstitial lung disease
"Source: Fingerlin TE, 2013"

1.5. RESEARCH SITUATION IN THE WORLD AND IN THE COUNTRY

In the world, there are many new studies on interstitial lung disease on the background of rheumatoid arthritis. Meihua Qiu's Synthetic Study. Records of factors associated with mortality in ILD associated with rheumatoid arthritis include: older age (HR = 1.04, 95% CI 1.03–1.05), male sex (HR = 1.44, 95% CI 1.21–1.73), history of smoking (HR = 1.42, 95% CI 1.03–1.96), lower pulmonary capacity for carbon monoxide (DLCO) % predicted (HRs = 0.98, 95% CI 0.97–1.00), exertion capacity (FVC)% predicted (HRs = 0.99, 95% CI 0.98–1.00), composite physiological index (CPI) (HRs = 1.04, 95% CI 1.02–1.06), pattern of common interstitial pneumonia (UIP) on HRCT (HRs = 1.88, 95% CI 1.14–3.10 and RRs = 1.90, 95% CI 1.50–2.39), emphysema present (HR = 2.31, 95% CI 1.58–3.39), and exacerbations of interstitial pulmonary disease (HRs = 2.70, 95% CI 1.67–4.36) were associated with increased mortality in interstitial lung disease on the background of rheumatoid arthritis, while rheumatic factor (RF) positivity was not relevant.

In Vietnam, research by Ta Thi Huong Trang evaluated some factors related to interstitial pneumonia in patients with rheumatoid arthritis including 212 patients with rheumatoid arthritis diagnosed according to ACR 1987 and/or ACR/EULAR 2010 criteria divided into 2 groups: Group 1 included 145 patients with rheumatoid arthritis without interstitial pneumonia, Group 2 includes 67 patients with rheumatoid arthritis with interstitial pneumonia identified according to the diagnostic criteria for interstitial pneumonia of ATS/ERS/JRS/ALAT 2011. In this study, the authors found an association between interstitial pneumonia and age: rheumatoid arthritis patients over 65 years old had a higher incidence of interstitial pneumonia than rheumatoid arthritis patients younger than 65 years old with $p<0.05$ and OR 1.95. Patients with rheumatoid arthritis who smoked had a higher incidence of interstitial pneumonia than the non-smoking group with a $p<$ of 0.05 and an OR of 3.3. Serum RF and anti-CCP levels were higher in the group of rheumatoid arthritis patients with interstitial pneumonia than in the group of rheumatoid arthritis patients without interstitial pneumonia with $p<0.05$. There was no association between interstitial pneumonia and gender, and the level of disease activity was $p>0.05$.

Chapter 2
OBJECTS AND METHODS OF RESEARCH

2.1. RESEARCH OBJECTIVES

1. Determination of ILD rate, clinical and subclinical characteristics and description of the rs35705950 variant of *MUC5B gene*, in patients with ILD.

2. Evaluation of the association between clinical, subclinical, rs35705950 variant of MUC5B gene, disease activity and 4 ILD phenotypes.

2.2. OBJECTS OF STUDY

All 306 patients with RA, of which 101 patients had ILD and 205 patients without ILD, were diagnosed, treated and monitored at the Department of Musculoskeletal Medicine at Gia Dinh People's Hospital during the period from 01/2023 to 05/2024.

2.2.1. Admission criteria

- Patient ≥ 18 years of age, diagnosed with RA according to EULAR/ACR 2010.
- With interstitial lung disease diagnosed on high-resolution CT images according to ATS/ERS/JRS/ALAT 2018.
- The patient agrees to participate in the study.

2.2.2. Exclusion criteria

- Patients with RA in combination with other autoimmune diseases.
- Patients arbitrarily take male drugs of unknown type or do not comply with treatment.
- The patient has been diagnosed with pneumonia with a positive sputum transplant result or is being treated for pneumonia diagnosed by a respiratory medicine specialist.
- Patients with contraindications to high-resolution CT scan: pregnancy, refusal of CT scan.
- Patients who had serious events due to medical conditions or accidents during the study period that resulted in death or prolonged mechanical ventilation.
- The patient drops out of the study in the middle of the study.

2.3. RESEARCH CONTENT AND LOCATION

2.3.1. Research time

The study is from 01/2023 to 05/2024.

2.3.2. Research location

Department of Musculoskeletal Medicine, Gia Dinh People's Hospital.

Department of Biochemistry and Hematology, Gia Dinh People's Hospital.

Department of Diagnostic Imaging, Gia Dinh People's Hospital.

Center for Molecular Biomedicine, University of Medicine and Pharmacy, Ho Chi Minh City.

2.4. RESEARCH METHODOLOGY

2.4.1. Research design

Cross-sectional research.

2.4.2. Sample size of the study

We calculated the sample size formula according to goal 1: ***Determining the prevalence of interstitial lung disease variants in RA*** patients.

The number of patients needed for the study was calculated based on the formula to estimate the sample size according to the proportion of disease in the population.

The sample size is calculated according to the following formula:

$$n = \frac{Z^2_{(1-\frac{\alpha}{2})} \times p(1-p)}{d^2}$$

Where p is the success rate, d is the marginal error, $Z(1-\alpha/2)$ is the probability of the normal distribution at the probability of error α.

- Probability of error $\alpha = 0.05$, then $Z(1-\alpha/2) = 1.96$.

- Author Ta Thi Huong Trang evaluated the clinical, subclinical characteristics and risk factors for ILD in patients with RA from 11/2015 to 3/2020 and recorded this rate as 31.6%--> choose p= 0.316

- d: accuracy (or allowable error), choose d = 0.1.

From the above formula, we calculated the sample size n selected from 84 RA patients with ILD or higher. In the study, we have obtained 101 patients with ILD → that meet the number of sample sizes

2.4.5. Collection Variables

2.4.5.1. Clinical

- Gender characteristics: there are 2 values: Male and Female.

- Age characteristics: show the average age and divide into age groups: < 40 years old, 40 – 49 years old; 50 – 59 years old; 60 – 69 years old and ≥ 70 years old.

- History of pulmonary diseases: Recording the patient's previous lung diseases includes the following values: pulmonary tuberculosis, bronchiectasis, lung damage due to covid, smoking. The covid lung injury variable is determined through the patient's medical records.

- History of RA:

- Clinical symptoms:

Shortness of breath levels: mMRC scale: includes 5 levels from 0 to 4

- Number of swollen joints, number of painful joints (according to DAS28) includes the following joints: shoulder joint, elbow joint, wrist joint, finger joint 1 to 5, proximal finger joint 1 to 5, knee joint (including both sides).

- VAS (Visual Analogue Score):

CDAI (clinical disease activity index)

SDAI (simplified disease activity index)

DAS 28 (Disease Activity Score With 28-Joint Counts)

2.4.5.2. Subclinical

Hematological indicators:

Evaluation of the staging of the disease according to Steinbrocker is based on motor function and X-ray damage of the joint:

High-Resolution CT Image Rating:

The extent of lung damage of ILD:

Pulmonary fibrosis pictures:

Other lesions of the lungs:

Lung Function Assessment:

2.8. Research Virtue

We conducted the research after obtaining the consent of the leaders of the Department of Musculoskeletal Internal Medicine and through the Medical Ethics Council at Gia Dinh People's Hospital and through the Medical Ethics Council of Hue University of Medicine and Pharmacy. Letter of approval with code H2022/519 dated 16/12/2022

Chapter 3
RESEARCH RESULTS

Through the study period from 04/2023 to 05/2024, we have collected 306 patients who have been examined and treated at the Department of Musculoskeletal Medicine - Gia Dinh People's Hospital, of which 205 patients have ILD and 101 patients have ILD with the following research characteristics:

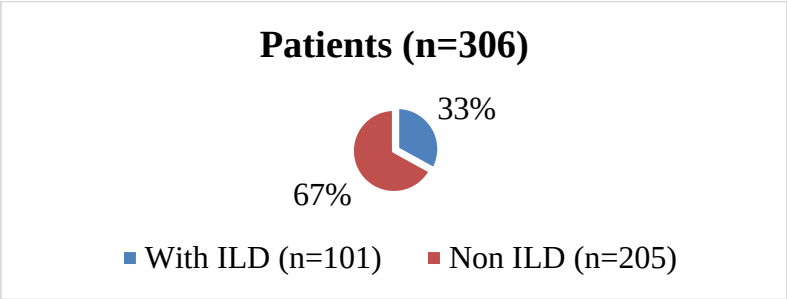

Figure 3.1: Percentage of RA with ILD

Remarks:

- It was recorded that 101 patients with ILD (accounting for 33%) were diagnosed through chest HRCT imaging.

3.1. CLINICAL AND SUBCLINICAL CHARACTERISTICS OF PATIENTS WITH INTERSTITIAL PULMONARY DISEASE AND THE RATE OF VARIATION RS35705950 OF *THE MUC5B GENE*

3.1.1. Clinical characteristics

Gender:

Table 3.1: Gender characteristics

		Patients with RA		P Value
		ILD group (n=101)	Non-ILD group (n=205)	
Gender	Male	9 (8,9)	29 (14,1)	0,192¶
	Female	92 (91,1)	176 (85,9)	

Age:

Table 3.2: Age characteristics

		Patients with RA		P Value
		ILD group (n=101)	Non-ILD group (n=205)	
Age Group	< 40	4 (4,0)	18 (8,8)	0,333¶
	40 - 49	10 (9,9)	20 (9,8)	
	50 – 59	40 (39,6)	62 (30,2)	
	60 - 69	30 (29,7)	72 (35,1)	
	≥ 70	17 (16,8)	33 (16,1)	
Average age		59.63 ± 11.51	58.57 ± 12.46	0,473‡

Table 3.6: Respiratory clinical symptoms

		Patients with RA		P Value
		ILD group (n=101)	**Non-ILD group (n=205)**	
Scale mMRC	Degree 0	37 (36,6)	167 (81,5)	**<0.001¶**
	Grade 1	50 (49,5)	32 (15,6)	
	Grade 2	10 (9,9)	2 (1,0)	
	Grade 3	1 (1,0)	3 (1,5)	
	Degree 4	3 (3,0)	1 (0,5)	

¶: Chi-squared test

Remarks:

- Patients with ILD had more respiratory symptoms than those without ILD, which was statistically significant. Dry cough accounted for 16.8% and shortness of breath accounted for 63.4%.

- In terms of the level of dyspnea in the ILD group, most of them were dyspnea of grade 1 according to mMRC, accounting for 49.5%. The group of patients with symptoms of moderate shortness of breath or higher accounted for 13.9%.

3.1.5. Assessment of the level of disease activity through scales

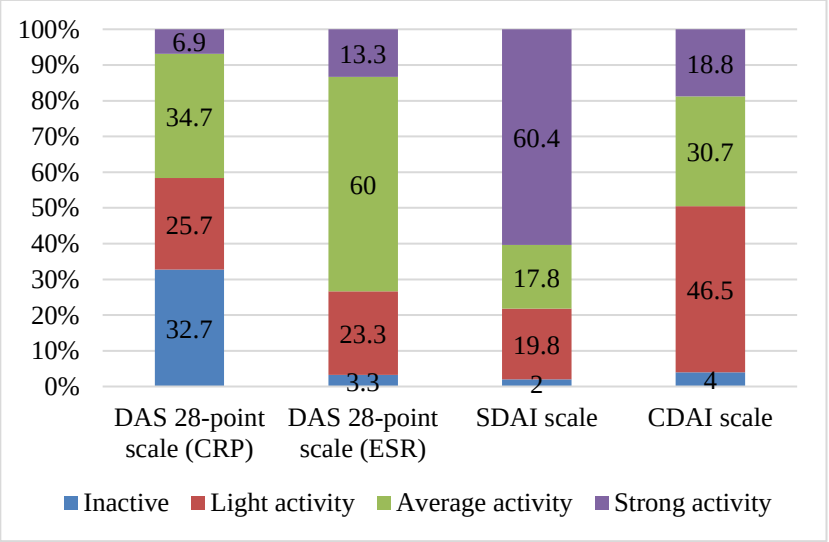

Figure 3.2: Disease activity level of the group of patients with ILD on scales

3.1.6. High-resolution chest HRCT image in the patient group with ILD

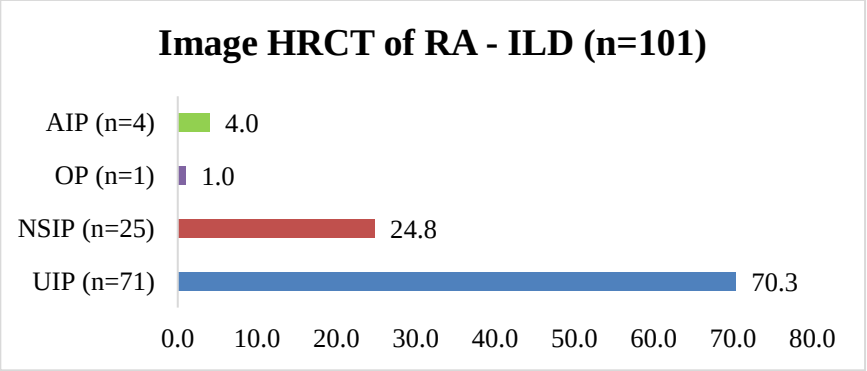

Figure 3.3: Image of ILD lesions in patients with chest disease on high-resolution chest HRCT

(UIP: Common interstitial pneumonia; NSIP: Atypical interstitial pneumonia; OP: Organized pneumonia of unknown origin)

3.1.8. Frequency of allele types in patients with rheumatoid arthritis with interstitial lung disease

Table 3.12: Frequency of allele types in the rheumatoid arthritis group with interstitial lung disease

		Allele types gene *MUC5B*			P Value
		GT (n=17)	**GG (n 289)**	**TT (n=0)**	
RA	ILD Group (n=101)	16 (15,8)	85 (84,2)	0	**<0.001**§
	Group without ILD (n=205)	1 (0,5)	204 (99,5)	0	
ILD lesion level	<= 10%	13 (81,2)	71 (84,5)	0	0.167§
	10,1 – 25%	1 (6,3)	11 (13,1)	0	
	>25%	2 (12,5)	2 (2,4)	0	

§: Fisher Accuracy Test

¶: Chi-squared test

3.1.9. Factors affecting the likelihood of suffering from ILD in patients with RA

We conducted a monovariable analysis of factors that are likely to affect the risk of BPMK in patients with BKDT.

3.2. ASSOCIATION BETWEEN CLINICAL, SUBCLINICAL, MUTANT RS35705950 MUC5B GENE, DISEASE ACTIVITY AND 4 ILD PHYNOTYPEs

3.2.1. Correlation of clinical characteristics with 4 ILD lesion phenotypes

Table 3.17: Clinical Relevance and ILD Lesion Pattern

		BPMK lesion morphology			**P Value**
		UIP (n=70)	**NSIP (n=24)**	**OP/AIP (n=7)**	
Group BMI > 25	Yes	17 (24,3)	3 (12,5)	4 (57,1)	0,05§
	None	53 (75,7)	21 (87,5)	3 (42,9)	
Respiratory symptoms	Cough	9 (12,9)	6 (25,0)	2 (28,6)	0,269
	Shortness of breath	43 (61,4)	17 (70,8)	4 (57,1)	0,668
mMRC Scale	Grade 0	27 (38,6)	7 (29,2)	3 (42,9)	**0,01**
	Grade 1	33 (47,1)	15 (62,5)	2 (28,6)	
	Grade 2	8 (11,4)	2 (8,3)	0 (0,0)	
	Grade 3	1 (1,4)	0 (0,0)	0 (0,0)	
	Degree 4	1 (1,4)	0 (0,0)	2 (28,6)	

3.2.4. Associations of the RS35705950 variant *of the MUC5B* gene with ILD lesion type

Table 3.23: Associations of the rs35705950 variant *of the MUC5B* gene with ILD lesion type

		ILD lesion morphology			**P Value**
		UIP (n=70)	**NSIP (n=24)**	**OP/ AIP (n=7)**	
Variant rs35705950 gene *MUC5B*	GT allele style	11 (15,7)	0 (0,0)	5 (71,4)	**<0,001§**
	GG allele type	59 (84,3)	24 (100,0)	2 (28,6)	

§: Fisher Accuracy Test

Remarks:

- Variants RS35705950 of the *MUC5B* gene tends to increase the rate of OP/AIP lesions in patients with statistically significant ILD.

Chapter 4
DISCUSSION

4.1.8. rs35705950 variant of *the MUC5B gene*

Although the exact mechanism by which RA-ILD occurs is unknown, genetic factors such as age, sex, race, and autoantibodies, rheumatoid factor (RF), and anti-cyclic citrullin peptide (CCP) antibodies (ACPA), have been suggested as risk factor. Some patients with rheumatoid arthritis may have genetic characteristics associated with ILD. Human leukocyte (HLA)-B54, HLA-DQ1B*0601, HLA-B40, HLA-DR4, and α-1 page-coding protease inhibitors increase the risk of ILD in rheumatoid arthritis, while HLA-DRB1 is associated with rheumatoid arthritis but reduces the incidence of RA with ILD has been demonstrated. Like other ILD, the inflammatory response activates cytokines, chemokines, and growth factors, such as tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and interleukin (IL) which have been shown to contribute to fibroblastic differentiation and proliferation, increased synthesis and deposition of extracellular matrix (ECM) and increased activity of matrix metallicoproteinase (MMP) leading to ILD. Fibroblasts in the synovial membrane play a similar role in the pathogenesis of articular manifestations in patients with RA.

Jeganathan et al. demonstrated that mortality rates associated with RA and RA-ILD vary significantly depending on the patient's race. Overall, the mortality rate associated with RA-ILD was highest among Hispanics (26% higher than whites), followed by whites, and lowest among blacks (27% lower than whites) in the United States between 2005 and 2018. Native Americans are more susceptible to RA than whites. Furthermore, drug-induced interstitial pneumonia is more frequent in the Japanese population than in people of other ethnic groups, and acute exacerbation of ILD is also more frequent in the Japanese population than in other ethnic groups.

CONCLUSION

1. Clinical and subclinical characteristics of patients with interstitial pulmonary disease and the rate of rs35705950 variant of *the MUC5B gene*

- The proportion of women accounts for the majority. The male-to-female ratio is 1:9. The average age of patients with ILD is 59.6 years. The age group from 50 to 59 years old accounted for the largest rate at 39.6%.

- The duration of disease for more than 5 years in the group of people with ILD is 42.5%. The duration of RA > 5 years is statistically significantly related to the rate of ILD.

- The rate of overweight and obese patients in the ILD group was 38.6%. Overweight and obese patients are associated with statistically significant ILD.

- Patients with ILD had more respiratory symptoms than those without ILD, which was statistically significant. Dry cough accounted for 16.8% and shortness of breath accounted for 63.4%. Most were dyspnea of grade 1 according to mMRC, accounting for 49.5%.

- 2/3 of patients with ILD have joint pain of 1-10 joints, and more than 1/2 of patients with ILD do not have swelling of the joints. Most of the mild pain levels according to the VAS scale accounted for 64.4%.

- Most of the hematological indicators, sedimentation rate, liver enzymes are within normal limits. There is no meaningful difference between the 2 groups of patient.

- 2/3 of patients with ILD present with common form of interstitial pneumonia (UIP) on high-resolution chest images. Atypical interstitial pneumonia (NSIP) imaging accounted for 24.8%. Images of organized pneumonia (OP) or disseminated acute inflammation are very rare, accounting for 1% and 4% respectively. Most patients have a level of interstitial lung damage of 5-10% of the lung volume and more than 1/2 of patients have an accompanying image of pulmonary fibrosis on the chest HRCT.

- 2/3 of patients have a normal FVC index. 18.7% of restrictive ventilation disorders were mild, 3.3% were moderate, and there was a linear association between the level of lung damage of ILD and FVC. The more severe the damage, the lower the FVC index.

- 2/3 of the patients with ILD measured the ability to diffusion CO gas with abnormalities through the DLCO index. The mild level accounted for 39.6%, the median level was 18.7%, and there was a linear association between the level of lung damage of ILD and the DLCO index. The more severe the damage, the lower the DLCO index

- No TT allele type was noted in the study population. The proportion of patients with GT allele type in RA patients was 17/306 cases, accounting for 5.6%. The study also showed the predominant presence of the G allele with a frequency of 97.22%, while the T allele accounted for a significantly lower proportion of 2.78%

- There was a statistically significant difference between the proportion of allele types in patients with and without ILD, with the group with ILD having a higher rate of *MUC5B gene variation* than the other group.

- There is no association between age and allele type in patients with rheumatoid arthritis with or without interstitial lung disease

- Univariate analysis shows that risk factors leading to ILD in patients with RA include:

+ Duration of RA > 5 years (OR = 1.92; p = 0.014)

+ Normal and mild activity level according to the DAS 28 CRP scale (OR=1.44, p = 0.003)

+ Variant rs35705950 on *the MUC5B* gene (OR= 3.2; p < 0.001)

2. Association between clinical and subclinical features, rs35705950 variant of *MUC5B* gene, DAS28 and FVC, DLCO activity with the degree of 4 interstitial lung phenotypes

- No statistically significant difference was recorded between ILD lesion type and clinical factors:

+ Gender, age group,

+ History of RA, symptoms of cough, shortness of breath

+ Number of swollen joints, pain and VAS scale,

+ Disease activity level according to the DAS28 CRP scale, and according to the SDAI scale

- The obese patient group (BMI > 25) had a higher tendency to develop OP/AIP than the other 2 groups

- The OP/AIP group had a higher rate of patients with moderate dyspnea than the other 2 groups, which was statistically significant

- No statistically significant differences were recorded between ILD lesion patterns and subclinical ones

+ Hematological indicators

+ FVC, DLCO indices

- In the UIP and NSIP groups, most of the lung damage on HRCT is 5-10%. 4 patients with acute pneumonia lesions all had a lesion of 10% or more. Acute pneumonia patients had a statistically significant higher level of lung damage than other groups

- The GT allele type of the RS35705950 variant of *the MUC5B* gene increases the incidence of OP/AIP lesions in patients with ILD.

RECOMMENDATIONS

Based on our research, we draw the following recommendations:

- The study should be continued after the thesis is completed with a larger sample size, multi-center study, and longitudinal follow-up to further assess the pulmonary fibrosis status in rheumatoid arthritis patients. This will provide more accurate prognostic factors and treatment guidelines for these patients.

- The rs35705950 variant of the MUC5B gene tends to be associated with the severity of septic shock, so genetic testing should be considered for prognostic purposes in rheumatoid arthritis patients with septic shock.

LIST OF PUBLISHED ARTICLES

1. Duong Minh Tri 2024, Survey of clinical characteristics and images of lung damage in patients with rheumatoid arthritis with interstitial lung disease, Hue Journal of Medicine and Pharmacy, University of Medicine and Pharmacy, Hue University – No. 5, vol. 14/2024, pp. 196-200
2. Duong Minh Tri 2024, Survey on the rate of mutation in the MUC5B gene and risk factors for the progression of interstitial pulmonary disease on rheumatoid arthritis, Vietnam Medical Journal Vol. 540- July – Thematic issue – 2024, pp. 167-172
3. Duong Minh Tri 2026, Research on factors related to interstitial pulmonary disease on rheumatoid arthritis, Vietnam Medical Journal vol. 588- January - No. 2 - 2026, pp. 330-334
4. Tri DT, Bao HB, Tu THK and et. Cluster analysis identifies distinct articular- and pulmonary-dominant phenotypes in rheumatoid arthritis. Open Rheumatol J. 2026. (in press)