European Review for Medical and Pharmacological Sciences 2024; 28: 3683-3696

Elevated peripheral blood monocyte count is associated with prolonged postoperative hospitalization and functional decline in patients with interstitial lung diseases undergoing surgical lung biopsy

T. KARAMPITSAKOS[1], T. MILAS[1,2], P. TSIRI[1], M. KATSARAS[1], E. KOLETSIS[3], K. VACHLAS[2], E. MALAKOUNIDOU[1], E. ZARKADI[1], G. TSIRIKOS[1], V. GEORGIOPOULOU[1], V. SOTIROPOULOU[1], E. KOULOUSOUSA[1], E. THEOCHARI[1], D. KOMNINOS[1], G. HILLAS[4], V. TZILAS[4], A. GOGALI[5], K. KOSTIKAS[5], P. BAKAKOS[6], I. VAMVAKARIS[7], F. SAMPSONAS[1], N. KOUMALLOS[8], D. BOUROS[6], A. TZOUVELEKIS[1]

[1]Department of Respiratory Medicine, University Hospital of Patras, Patras, Greece
[2]Department of Thoracic Surgery, General Hospital for Thoracic Diseases "SOTIRIA", Athens, Greece
[3]Department of Cardiothoracic Surgery, University Hospital of Patras, Patras, Greece
[4]5th Department of Respiratory Medicine, General Hospital for Thoracic Diseases "SOTIRIA", Athens, Greece
[5]Department of Respiratory Medicine, University Hospital of Ioannina, Ioannina, Greece
[6]1st Academic Department of Respiratory Medicine, General Hospital for Thoracic Diseases "SOTIRIA", Athens, Greece
[7]Department of Pathology, General Hospital for Thoracic Diseases "SOTIRIA", Athens, Greece
[8]Cardiac Surgery Department, Hippokration General Hospital of Athens, Greece

T. Karampitsakos and T. Milas equally contributed to this work

Abstract. – OBJECTIVE: Monocyte count and red cell distribution width (RDW) have shown prognostic potential in patients with fibrotic lung diseases. Their kinetics and prognostic usefulness of peripheral blood indices in patients with interstitial lung diseases (ILDs) undergoing surgical lung biopsy for diagnostic reasons have not been studied.

PATIENTS AND METHODS: We retrospectively included consecutive patients with ILD who underwent surgical lung biopsy for diagnostic purposes Between 07/11/2019 and 11/10/2022.

RESULTS: Fifty-five (n=55) patients were included in the study. Median age was 65.0 years (95% CI: 63.0 to 66.0). Postoperative peripheral blood monocyte count on Day 1 was significantly higher compared to preoperative, perioperative, and postoperative values on Day 90 (repeated measures ANOVA, $p<0.0001$). Patients in the high postoperative monocyte count group had significantly increased length of postoperative hospital stay [Mann-Whitney test, $p=0.007$] and significantly lower Forced Vital Capacity (FVC)% predicted 3 months after surgery [Mann-Whitney test, $p=0.029$] compared to patients in the low postoperative monocyte count group. Postoperative RDW on Day 90 was significantly higher compared to preoperative, perioperative and postoperative-Day 1 RDW (repeated measures ANOVA, $p=0.008$, $p=0.006$, $p<0.0001$, respectively). Patients in the high postoperative RDW group did not have increased hospital stay (Mann-Whitney test, $p=0.49$) or decreased FVC% predicted at 3 months compared to patients in the low postoperative RDW group (Mann-Whitney test, $p=0.91$).

CONCLUSIONS: Peripheral blood monocyte count could be a prognostic biomarker for patients with ILDs undergoing diagnostic surgical lung biopsies. RDW does not seem to represent an acute phase biomarker but seems to increase over time following disease progression. Larger studies are urgently required.

Key Words:
Monocyte count, Red cell distribution width, Surgical lung biopsy.

Corresponding Authors: Fotios Sampsonas MD, Ph.D; e-mail: fsampsonas@upatras.gr
Argyrios Tzouvelekis MD, Ph.D; e-mail: atzouvelekis@upatras.gr, argyris.tzouvelekis@gmail.com

Introduction

Interstitial lung diseases (ILDs) represent a heterogeneous group of lung disorders characterized by a varying degree of inflammation and fibrosis of the pulmonary parenchyma[1]. A classification suggested by the recent American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax (ATS/ERS/JRS/ALAT) guidelines is the following: 1) exposure-related ILDs such as hypersensitivity pneumonitis and drug-induced ILDs, 2) autoimmune-ILDs such as rheumatoid arthritis-ILD and systemic sclerosis associated-ILD, 3) idiopathic interstitial pneumonias such as Idiopathic Pulmonary Fibrosis (IPF), 4) sarcoidosis and 5) ILDs with cysts and/or airspace filling such as pulmonary alveolar proteinosis and pulmonary Langerhans Cell Histiocytosis[2,3]. The disease course of the aforementioned entities is highly heterogeneous and could vary from totally reversible disease to progressive pulmonary fibrosis. Timely diagnosis is crucial, considering that timely management might lead to remission or substantially slow disease progression[4,5].

Despite their heterogeneous background, ILDs share common clinical and radiographic features; thus, establishing a definite and timely diagnosis is challenging[6]. A working diagnosis is often set even in reference centers following multidisciplinary discussion[7]. Based on that, although the role of histology is limited compared to the past, obtaining lung tissue for diagnostic purposes is still needed in a proportion of cases. However, procedure-related mortality of Video Assisted Thoracic Surgery (VATS) in patients with ILDs is not negligible[8,9]. If VATS is implemented on a non-elective basis in ILDs, mortality might be even up to 16%. This percentage is substantially higher compared to the respective percentage (1.7%) observed following an elective strategy[10,11].

Biomarkers able to predict negative outcomes in patients with ILDs who are candidates for surgical lung biopsy could pave the way towards further reduction of adverse outcomes. We have previously shown that increased monocyte count and red cell distribution width (RDW) are negative prognostic markers in patients with IPF[12]. Increased peripheral blood monocyte count was linked to a higher risk of disease progression, hospitalization, and mortality in multiple IPF cohorts[12-15]. The prognostic role of peripheral blood monocyte count has been recently extended to other fibrotic ILDs[16]. Increased RDW has been suggested as a negative prognostic indicator in multiple lung diseases[17,18].

Thus, the concept of investigating the kinetics and prognostic potential of these two biomarkers in patients with ILDs undergoing diagnostic surgical lung biopsy seems rational. The aim of our study was to investigate changes in peripheral blood monocyte count and RDW during the pre/postoperative period and determine if increased values could have a prognostic value in patients with ILDs undergoing surgical lung biopsies for diagnostic purposes.

Patients and Methods

Study Design and Oversight

This was an observational, retrospective study. We included consecutive patients with interstitial lung disease (ILD) who underwent surgical lung biopsy for diagnostic purposes following a multidisciplinary discussion of clinical, serologic, radiologic, and functional data between November 7, 2019, and October 11, 2022. Diagnosis of ILD was based on ATS/ERS/JRS/ALAT Clinical Practice Guidelines[19-22]. Patients were treatment-naïve in the context of ILD management. Patients with malignancies were excluded from this study. Epidemiological data were derived from two independent cohorts (General Hospital for Thoracic Diseases "SOTIRIA" Athens and Department of Thoracic Surgery, University Hospital of Patras). The study was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonisation E6 guidelines for Good Clinical Practice, and local regulations. Retrospective data collection and analysis were approved by the Institutional Review Board and the Local Ethics Committee (protocol number: 23322/24-11-16, 27448/22-11-19). Written informed consent was obtained from each patient before the surgical procedure.

For each patient, we recorded demographics, including age, gender, functional indices preoperative and postoperative (Day 90), peripheral blood monocyte count and RDW at 4 different time points (preoperative, perioperative, postoperative Day 1, postoperative Day 90), length of hospital stay, and histologic diagnosis.

Surgical Lung Biopsy

The protocol followed for surgical lung biopsy was either the protocol of open lung biopsy or the protocol of VATS. Both protocols are described below:

Open lung biopsy

This surgical approach is performed under general anesthesia. Initially, a small anterior limited thoracotomy is performed typically in the fourth or fifth interspace. The muscle layers are prepared, and subsequently, the ribs are carefully separated in order to gain access to the thoracic cavity. Previously, the biopsy was conducted using a running catgut suture technique in two rows. However, with the advancement of stapling devices, this procedure has become faster and safer for patients. In cases where the placement of a gastrointestinal anastomosis stapler is not feasible, alternative devices such as transverse anastomosis (TA)-30 or TA-55 can be used. Almost all lung surgeries utilize one-lung ventilation anesthesia (OLV) with the insertion and monitoring of double-lumen tubes (DLTs), which is the standard method used to ventilate one lung and collapse the other. OLV typically improves the entrance to the thoracic cavity and greatly enhances the quality of the intervention procedure itself. After the surgery, the chest wound is closed in layers, and a drainage tube is inserted into the thoracic cavity. After extubation, which is usually performed in the operating room, the patient is moved to the recovery room for monitoring of vital signs during the first period after anesthesia. The patient typically spends twenty minutes to half an hour in the recovery room before being transferred to the department. However, if the patient has multiple comorbidities, they may need to stay in the intensive care unit for at least 1 day.

VATS

This minimally invasive procedure involves a thoracoscope, a thin tube with a camera, to visualize the lung. Multiple small incisions are made to introduce surgical instruments and the thoracoscope, thus allowing a more precise and less invasive approach compared to open lung biopsy. A variation of VATS, denominated Uniportal VATS, refers to a surgical procedure done through a single small incision in order to further reduce trauma and scarring. Both VATS and Uniportal VATS are presented below.

VATS became the preferred surgical method in case surgical lung biopsy is needed for the general population, including patients with ILDs. VATS can be performed under general anesthesia, thoracic epidural anesthesia, or intercostal block. Similarly to the aforementioned, VATS is typically performed through OLV with the placement and monitoring of DLTS. This is a standard method with which we achieve ventilating one lung and collapsing the other. OLV in VATS improves the entrance to the thoracic cavity and greatly enhances the quality of the intervention procedure. Typically, three trocars are strategically placed in an equilateral triangle configuration, with the lesion located at the apex. The first port is used for the thoracoscope and is positioned at the 7th intercostal space in the mid-axillary line. A working window of approximately 3-4 cm is created at the 5th-6th intercostal space in the mid-clavicular line. Finally, the last port is created at the 6th-7th intercostal space in the post-scapular area. Based on that, VATS provides a comprehensive view of the chest cavity, allowing for a thorough examination. This minimally invasive surgical technique offers several advantages, i.e., enhanced safety, reduced patient discomfort, shorter hospital stays, and comparable diagnostic efficacy to the traditional open method. After extubation, which is typically performed in the operating room, the patient is transferred to the recovery room for monitoring of vital signs during the first period after anesthesia. Usually, the patient stays in the recovery room for twenty minutes to half an hour and then is transferred to the department unless the patient has multiple comorbidities and thus remains in the intensive care unit for at least 1 day[23].

Uniportal VATS

Uniportal video-assisted thoracic surgery offers an alternative approach for lung biopsy, utilizing a single port incision measuring approximately 2-2.5 cm in length. The patient is typically positioned in lateral decubitus during the procedure. Although the exact placement of the port may vary, most surgeries involve a small incision in the 5th intercostal space along the mid-axillary line. Similar to standard VATS, Uniportal VATS involves the introduction of a lung grasper, an endostapler, and a video-thoracoscope with a 5 mm 30-degree optical source into the thoracic cavity. However, Uniportal VATS achieves an even higher level of minimally invasive access by utilizing only one intercostal space. The Uniportal VATS technique has shown multiple benefits, including reduced postoperative pain and faster recovery compared to the traditional VATS technique. These advantages contribute to the increasing utilization of Uniportal VATS in contemporary medical practice[23].

Outcome Measures

Outcome measures included: 1) differences in pre/postoperative peripheral blood monocyte count and RDW, 2) differences in peripheral blood monocyte count and RDW in patients undergoing Video Assisted Thoracic Surgery (VATS) and open thoracotomy, 3) associations of postoperative peripheral blood monocyte count, RDW with length of hospitalization and functional indices including FVC% predicted, and 4) the histologic diagnoses yielded.

Statistical Analysis

Continuous data were reported as mean± standard deviation (SD) or medians [95% Confidence Interval (CI)] depending on the presence or absence of normality following the Kolmogorov-Smirnov test. ANOVA repeated measures were used to investigate differences in monocyte count at the 4 different time points. An independent samples *t*-test or Mann-Whitney test was performed for the rest of the outcome measures based on the presence or absence of normality. In particular, patients were divided into subgroups based on the median value of monocyte count and RDW (high and low groups). Mann-Whitney test or independent samples *t*-test was applied to assess differences in Forced Vital Capacity % predicted (FVC% pred) and postoperative hospitalization between subgroups of patients split by the median value of complete blood count (CBC) parameter. *p*-values <0.05 were considered significant. The MedCalc v. 22.021 software (Tampa, FL, USA) was used.

Results

Baseline Characteristics

Fifty-five (n=55) patients were included in the study. Most patients were males (n=43, 78.2%), while 12 patients were females (21.8%). Median age was 65.0 years (95% CI: 63.0 to 66.0). Baseline characteristics are summarized in Table I. Median FVC% predicted and FEV1% predicted were 70.9 (95% CI: 66.0 to 76.7) and 75.6 (95% CI: 71.9 to 85.7), respectively. The mean preoperative monocyte count±SD was 0.59±0.24 K/μL. Mean preoperative RDW±SD was 13.04±1.89 (%).

Forty patients (n=40, 72.7%) underwent VATS, while fifteen patients (n=15, 27.3%) underwent open thoracotomy. The most common histologic pattern was usual interstitial pneumonia (UIP) (n=27, 49.1%), while the second most common was organizing pneumonia (n=18, 32.7%). Four patients were diagnosed with hypersensitivity pneumonitis (7.3%), 2 patients with lymphocytic interstitial pneumonia (3.6%), while 1 patient (1.8%) was diagnosed with each of the following diagnoses: lymphocytic interstitial pneumonia, non-specific interstitial pneumonia, pleuroparenchymal fibroelastosis, respiratory bronchiolitis-associated interstitial lung disease.

Table I presents the frequency of each histologic pattern. Overall, the median postoperative length of hospitalization was 2.0 days (95% CI: 2.0 to 2.24). Regarding adverse events, air leak was identified in 4 patients (7.3%).

Table I. Baseline characteristics.

Characteristics	(N, %)
Total number of patients	55
Male/Female	43 (78.2%) /12 (21.8%)
Current/Ever/ Never smokers	6 (10.9%)/37 (67.3%)/12 (21.8%)
Age (median, 95% CI)	65.0 (95% CI: 63.0 to 66.0)
FVC% predicted	70.9 (66.0 to 76.7)
FEV1% predicted	75.6 (71.9 to 85.7)
Usual Interstitial Pneumonia	27 (49.1%)
Organizing pneumonia	18 (32.7%)
Hypersensitivity pneumonitis	4 (7.3%)
Lymphocytic interstitial pneumonia	2 (3.6%)
Lymphangioleiomyomatosis	1 (1.8%)
Non-specific interstitial pneumonia	1 (1.8%)
Pleuroparenchymal fibroelastosis	1 (1.8%)
Respiratory bronchiolitis-associated interstitial lung disease	1 (1.8%)

FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second.

Monocyte Count Increases Following Thoracic Surgery

Postoperative monocyte count on Day 1 was significantly higher compared to preoperative, perioperative and postoperative values on Day 90 (repeated measures ANOVA, mean ± standard error: preoperative monocyte count: 0.59±0.03 K/μL, perioperative monocyte count: 0.52±0.04 K/μL, postoperative Day 1: 0.90±0.05 K/μL, postoperative Day 90: 0.61±0.02 K/μL, $p<0.0001$), (Figure 1A). Postoperative change in monocyte count was significantly higher in patients who

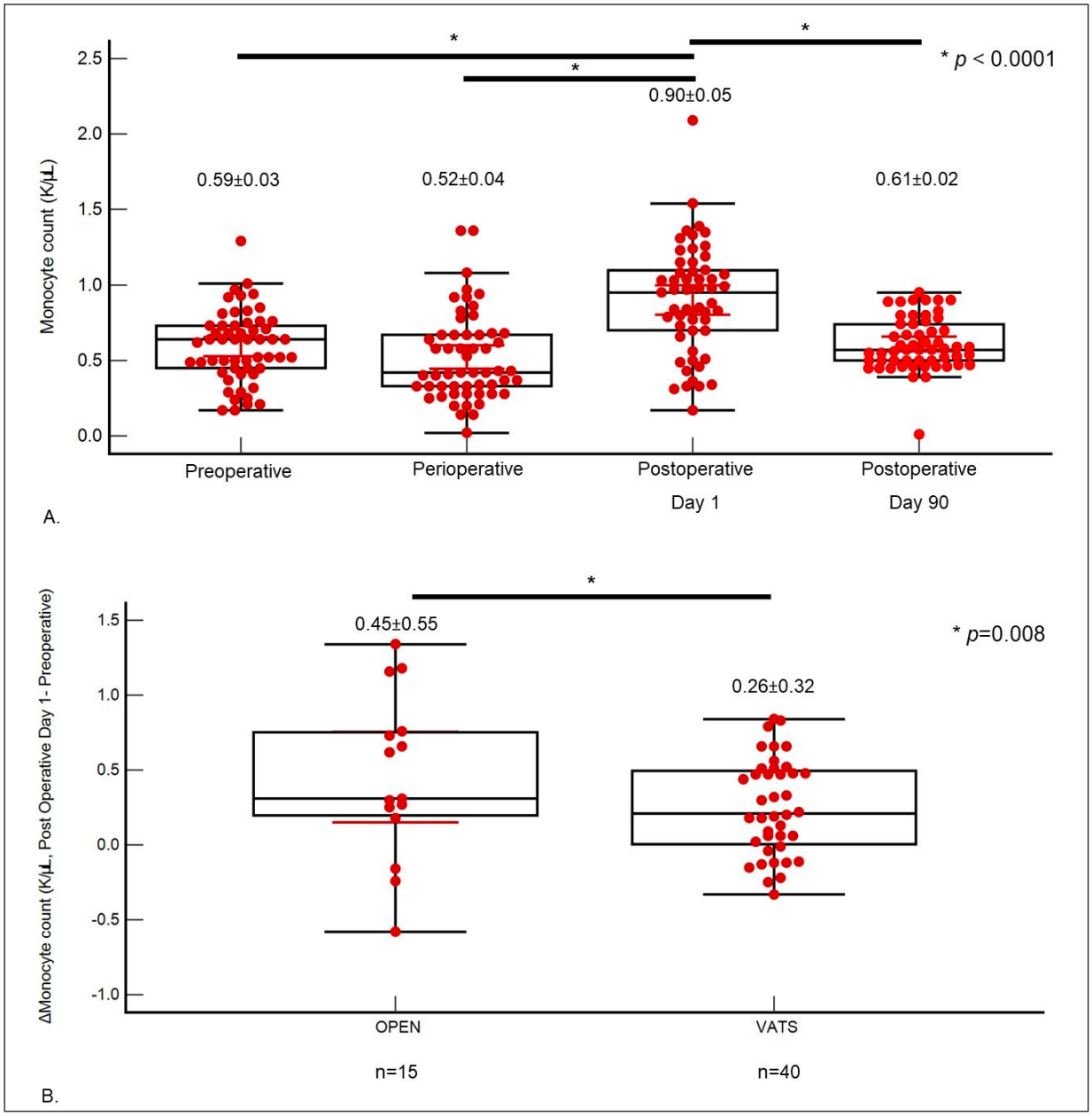

Figure 1. Plot derived from the comparison of monocyte counts in four different time points through repeated measures ANOVA. Postoperative monocyte count on Day 1 was significantly higher compared to preoperative, perioperative and postoperative values on Day 90 (Repeated measures ANOVA, mean ± standard error: preoperative monocyte count: 0.59±0.03 K/μL, perioperative monocyte count: 0.52±0.04 K/μL, postoperative Day 1: 0.90±0.05 K/μL, postoperative Day 90: 0.61±0.02 K/μL, $p<0.0001$) (**A**). Data comparison graph between patients that underwent open surgery and VATS with regards to change in monocyte count. Postoperative change in monocyte count was significantly higher in patients who underwent open thoracotomy compared to patients who underwent VATS (Independent samples *t*-test, open thoracotomy: 0.45±0.55, VATS: 0.26±0.32, $p=0.008$) (**B**). *: Significant *p*-values.

Table II. Multiple regression analysis for multiple predictors and postoperative monocyte count.

	Postoperative monocyte count		
Parameter	Coefficient	Std error	*p*-value
Age	0.003542	0.005469	0.5203
Diagnosis	0.01000	0.07275	0.8912
Smoking	0.07546	0.1168	0.5213
CRP	2.2233	11,023,810.0591	1.0000
Neutrophil count preoperative	0.01312	0.02586	0.6142
Neutrophil count postoperative	-0.007258	0.01464	0.6222

CRP: C-reactive protein.

underwent open thoracotomy compared to patients who underwent VATS (Independent samples *t*-test, open thoracotomy: 0.45±0.55, VATS: 0.26±0.32, p=0.008), (Figure 1B). Multiple regression showed that parameters including age, diagnosis, smoking status, neutrophil count, and CRP were not independently associated with postoperative monocyte count (Table II).

Increased Postoperative Peripheral Blood Monocyte Count Predicts Length of Hospitalization and Functional Decline

Patients in the high postoperative monocyte count group had significantly increased length of postoperative hospitalization compared to patients in the low postoperative monocyte count group [Mann-Whitney test, high monocyte count: 3.0 days (95% CI: 2.0 to 3.0), low monocyte count: 2.0 days (95% CI: 2.0 to 2.0), p=0.007], (Figure 2A). Multiple regression analysis showed that postoperative monocyte count was independently associated with postoperative hospitalization days (p=0.0228) (Table III). Patients in the high postoperative monocyte count group had significantly lower FVC% predicted 3 months postoperatively than patients in the low postoperative monocyte count group [Mann-Whitney test, high monocyte count: 75.0 (95% CI: 63.9 to 82.1), low monocyte count: 84.0 (95% CI: 76.4 to 97.0), p=0.029] (Figure 2B). Multiple regression analysis showed that postoperative monocyte count was independently associated with post-3 months FVC% predicted (p=0.0114) (Table IV).

RDW Increases During Disease Course

Postoperative RDW on Day 90 was significantly higher compared to preoperative, perioperative, and postoperative-Day 1 RDW [repeated measures ANOVA, mean ± standard error: postoperative RDW on Day 90: 14.04±0.31, *vs*. preoperative RDW: 13.04±0.25 (p=0.008), *vs*. perioperative: 12.78±0.28 (p=0.006), post-operative-Day 1: 12.61±0.25 (p<0.0001)] (Figure 3A). Postoperative change in RDW was significantly higher in patients undergoing open surgery compared to VATS (0.05, 95% CI: -0.33 to 0.30, *vs*. -0.27, 95% CI: -0.99 to -0.12, p=0.04), (Figure 3B). Patients in the high postoperative RDW group did not have increased hospital stay (Mann-Whitney test: 2.0 days, 95% CI: 2.0 to 2.0, *vs*. 2.0 days, 95% CI: 2.0 to 2.6, p=0.49) or decreased FVC% predicted at 3 months compared to patients in the low postoperative RDW group (Mann-Whitney test: 76.9, 95% CI: 64.0 to 95.1, *vs*. 81.4, 95% CI: 72.0 to 87.0, p=0.91).

Discussion

To the best of our knowledge, this is the first study showing that peripheral blood monocyte count increased following thoracic surgery, and high postoperative monocyte count is a negative prognostic indicator for patients with ILDs undergoing thoracic surgery for diagnostic purposes. Our data supports already published literature showing strong associations between surgical interventions[24,25] and ILD acute exacerbations as well as elevated peripheral blood monocytes with worse clinical outcomes[12,14].

In particular, we showed that postoperative monocyte count significantly increased compared to pre- and perioperative values. Importantly, we showed that values decreased again, as indicated by postoperative monocyte count on Day 90. The concept that monocyte count increases following lung tissue manipulation is further corroborated by the fact that postoperative monocyte count was significantly increased in patients undergoing open thoracotomy compared to patients who underwent VATS. On the contrary, RDW values increase over time as the disease progresses, and

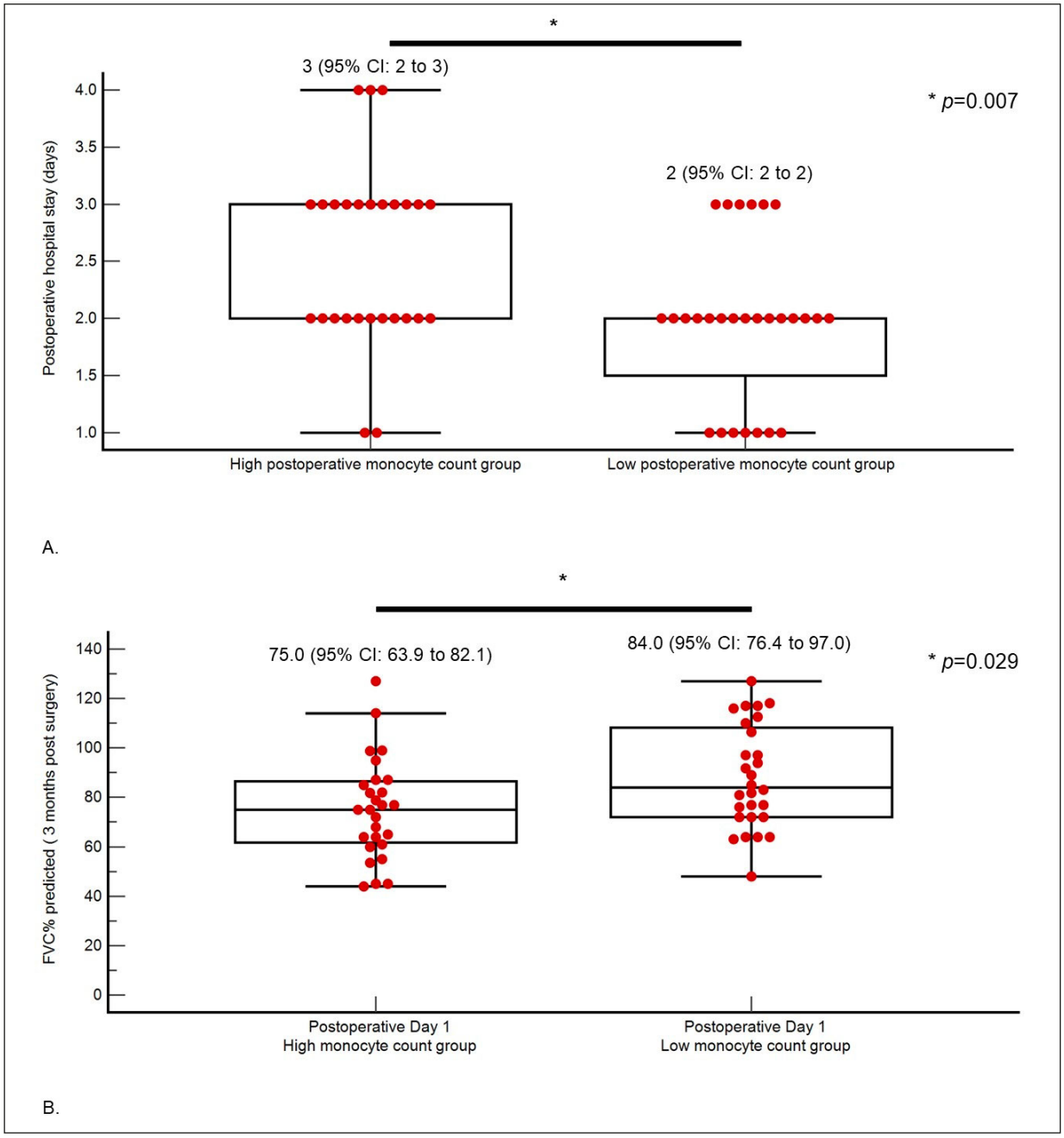

Figure 2. Data comparison graph between patients in the high and low postoperative monocyte count group with regards to the length of postoperative hospital stay. Patients in the high postoperative monocyte count group had significantly increased length of postoperative hospitalization compared to patients in the low postoperative monocyte count group [Mann-Whitney test, high monocyte count: 3.0 days (95% CI: 2.0 to 3.0), low monocyte count: 2.0 days (95% CI: 2.0 to 2.0), p=0.007], (**A**). Data comparison graph between patients in the high and low postoperative monocyte count group with regards to FVC% predicted 3 months following surgery. Patients in the high postoperative monocyte count group had significantly lower FVC% predicted 3 months postoperatively compared to patients in the low postoperative monocyte count group [Mann-Whitney test, high monocyte count: 75.0 (95% CI: 63.9 to 82.1), low monocyte count: 84.0 (95% CI: 76.4 to 97.0), p=0.029] (**B**). *: Significant p-values.

thus, RDW seems to be a biomarker of chronic illness and/or chronic hypoxia rather than an acute phase biomarker. Overall, postoperative monocyte count predicted the length of hospital stay and functional status of 3 months following thoracic surgery. The aforementioned highlights and extends the prognostic role of peripheral blood monocyte count in patients with ILDs.

Table III. Multiple regression analysis for multiple predictors and postoperative hospitalization days.

	Postoperative hospitalization days		
Parameter	**Coefficient**	**Std error**	***p*-value**
Age	0.0004767	0.01168	0.9676
Diagnosis	0.03188	0.1548	0.8377
Smoking	-0.09976	0.2495	0.6911
Monocyte count postoperative	0.7225	0.3070	**0.0228**
CRP	-3.3793	24,937,145.2622	1.0000
Neutrophil count preoperative	0.005097	0.05516	0.9268
Neutrophil count postoperative	-0.01388	0.03121	0.6586

CRP: C-reactive protein.

Table IV. Multiple regression analysis for multiple predictors and FVC% predict.

	FVC% predicted (3 months post surgery)		
Parameter	**Coefficient**	**Std error**	***p*-value**
Age	0.5041	0.2795	0.0777
Diagnosis	5.1310	3.7023	0.1723
Smoking	-2.6737	5.9682	0.6562
Monocyte count postoperative	-19.3300	7.3444	**0.0114**
CRP	229.0109	596,512,908.7524	1.0000
Neutrophil count preoperative	-1.6725	1.3196	0.2112
Neutrophil count postoperative	-2.1073	0.7466	**0.0070**

CRP: C-reactive protein, FVC: forced vital capacity.

The prognostic value of monocyte count with regard to mortality in IPF has been established in several studies[12,13,26-28]. A large, retrospective study including 7,459 patients with IPF demonstrated that patients with monocyte count ≥0.95 K/μL had higher all-cause mortality compared to patients with monocyte count <0.95 K/μL[13]. Pooled analysis of patients with IPF enrolled in pirfenidone trials (n=2,067) demonstrated increased 1-year risk of disease progression, all-cause hospitalization, all-cause mortality for patients with IPF and monocyte count above 0.95 K/μL or between 0.60-0.95 K/μL[14]. The same cut-off thresholds predicted mortality in the real-life study of 489 patients conducted in Greece and Germany[12]. The aforementioned are in line with the results of this study and provide a logical explanation for our findings.

Our findings could hopefully fuel larger studies and establish the role of peripheral blood monocyte count in patients with ILDs undergoing surgical lung biopsy. To this end, a clinically applicable biomarker for this group is an unmet need[29]. Aggregate risk scores based on clinical parameters or independent clinical parameters have been suggested[9,30-33]. However, risk stratification does not differ considerably compared to the general population[34]. Limitation of the likelihood of adverse events is not based on risk stratification but on specific precautions such as low-tidal volume ventilation, perioperative avoidance of high fraction of inspired oxygen (FiO_2), avoidance of fluid overload intake, avoidance of open surgeries, reduced duration of one-lung ventilation and minimal tissue manipulation[25,35-38]. Implementation of monocyte count in the risk stratification of these patients may further minimize adverse outcomes or highlight the need for meticulous evaluation of specific patients undergoing surgical lung biopsy.

The expanding prognostic role of monocytes in interstitial lung diseases couples with recent high-quality experimental evidence. Cellular deconvolution of the validated 52-gene signature in the peripheral blood that predicts mortality in IPF showed that the 7 upregulated genes (*PLBD1*, *TPST1*, *MCEMP1*, *IL1R2*, *HP*, *FLT3*, *S100A12*) are expressed in monocytes[13,39]. Emerging evidence shows that the role of monocytes is not restricted to

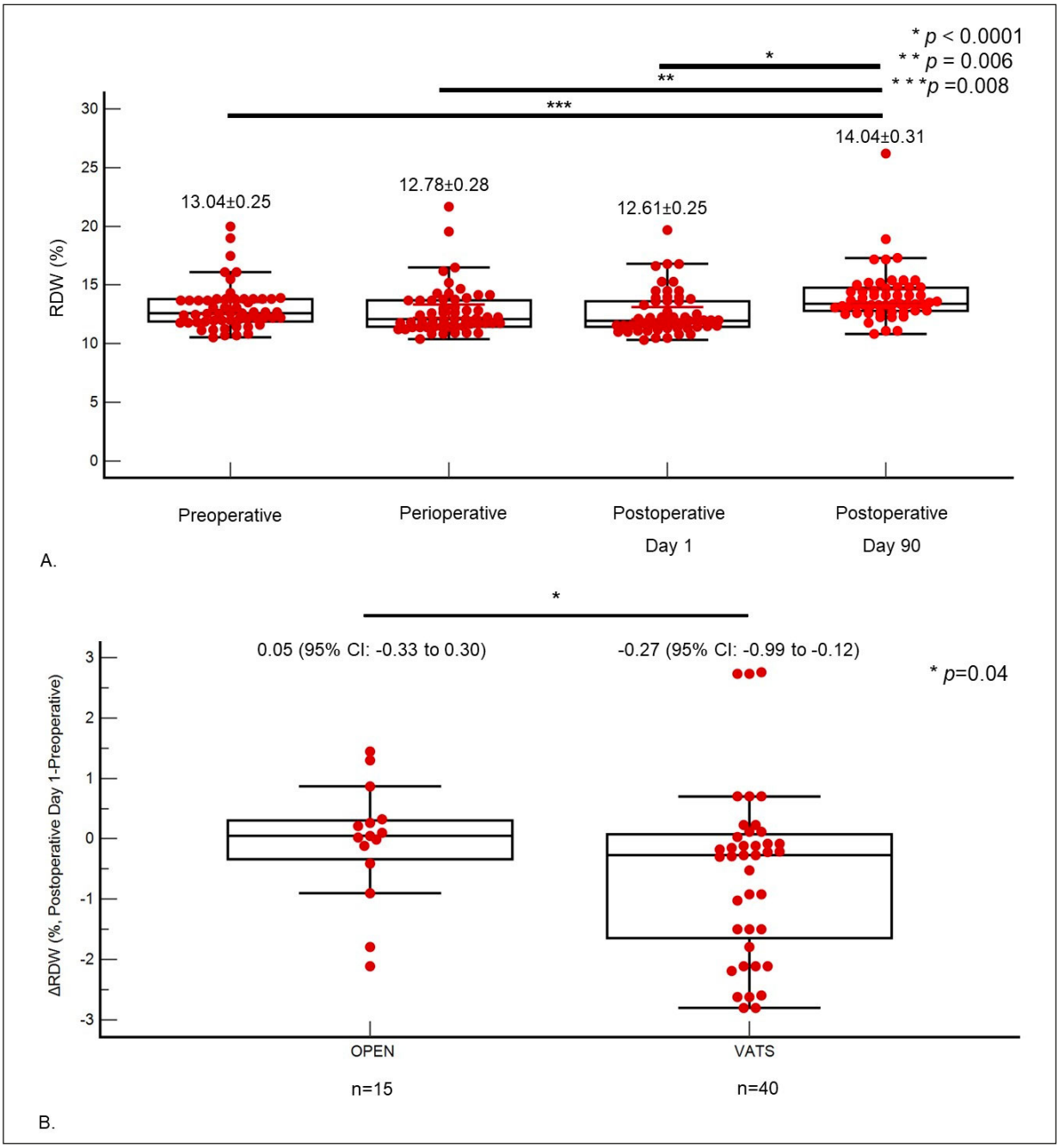

Figure 3. Plot derived from the comparison of RDW in four different time points through repeated measures ANOVA. Postoperative RDW on Day 90 was significantly higher compared to preoperative, perioperative and postoperative-Day 1 RDW [Repeated measures ANOVA, mean ± standard error: postoperative RDW on Day 90: 14.04±0.31, *vs.* preoperative RDW: 13.04±0.25 (p=0.008), *vs.* perioperative: 12.78±0.28 (p=0.006), post-operative-Day 1: 12.61±0.25 (p<0.0001)] (**A**). Data comparison graph between patients that underwent open surgery and VATS with regards to change in RDW. Postoperative change in RDW was significantly higher in patients undergoing open surgery compared to VATS (0.05, 95% CI: -0.33 to 0.30, *vs.* -0.27, 95% CI: -0.99 to -0.12, p=0.04) (**B**). *: significant p-values; ** and *** significant p-values for different comparisons.

prognosis. Monocytes seem to have a cardinal role in the pathogenesis of pulmonary fibrosis, as they seem to migrate from the bone marrow to the injured lung (possibly even if the injury of the tissue is associated with a thoracic surgery) and subsequently differentiate into pro-fibrotic macrophages and maybe into fibroblasts[40-47]. Several recent translational and experimental studies have shown

the derivation of different populations of alveolar macrophages and circulating fibrocytes from the monocyte cell lineage[43,44,48,49]. For example, extravasating CD14^{+} monocytes could be a source of interstitial and alveolar macrophages. In contrast, non-classical CD14^{lo} CD16^{+} monocytes seem to be mainly confined to the pulmonary vasculature and typically give rise to another population, named pulmonary intravascular macrophages[50]. Monocyte-derived lung macrophages, as well as lung resident alveolar macrophages, seem to be the macrophages that are most tied to the pathogenesis of pulmonary fibrosis. Moreover, single-cell RNA sequencing analysis showed a novel subset of macrophages, CX3CR1^{+}SiglecF^{+}, which seems to have a cardinal role for the fibrogenesis following injurious stimuli[51]. Recent data[52] have demonstrated that compartmental fractalkine imbalance had a role in the migration of CX3CR1^{+} monocytes into scar tissue. Finally, a cytokine produced by monocytes and macrophages, C-C motif chemokine ligand 18, has been proposed as a blood biomarker able to predict outcomes in patients with IPF[53].

Contrary to peripheral blood monocyte count, our results for RDW do not support its use as an acute phase biomarker and specifically as a prognostic biomarker for patients with ILDs undergoing surgical lung biopsy. Besides, the fact that increased RDW has been reported as a negative prognostic biomarker in multiple lung diseases, including IPF[12,27], COPD[18,54], and COVID-19[17,55,56] suggests that it might not be mechanistically linked with the aberrant wound healing of pulmonary fibrosis, but it rather represents a marker of general illness and/or tissue hypoxia[18]. Its slow change over time and association with hypoxia could be supported by current pathophysiologic evidence. First, the life cycle of red blood cells typically ranges between 100-120 days. This could explain the substantial time needed for profound changes in RDW values[57]. Secondly, erythropoietin represents one of the major determinants of RDW, as it regulates both the maturation and survival of erythrocytes[58]. Decreased partial pressure of oxygen leads to erythropoietin secretion by the renal cortex into circulation[58]. Given that disease progression in these patients is associated with worsened oxygenation, the aforementioned could be an explanation for the fact that RDW increased over time in the non-acute setting after surgery in our cohort. However, this hypothesis remains to be addressed in future studies, as the assumption that RDW increases over time following disease progression cannot be totally justified with these results, given that numerous conditions can influence RDW.

Our study has some limitations. First, this study presents the inherent weaknesses of a retrospective study. Secondly, the sample size is moderate, and due to power, we could not do other subgroups analysis, i.e., in UIP and non-UIP patients; yet the sample size is acceptable for this rare population of patients with ILDs in need of surgical lung biopsy for diagnostic purposes, especially within the era of a multi-disciplinary approach. Larger studies could provide further insights for specific subgroups of patients. Importantly, larger studies could provide fruitful insights into the prognostic role of specific subsets of monocytes such as CD14^{+}HLA-DR^{hi}CD163^{-}, CD14^{+}HLA-DR^{low}CD163^{-}, CD14^{+}HLA-DR^{low}CD163^{+} or MCEMP1^{+} monocytes through single-cell RNA seq or flow cytometry towards a precision medicine approach[59].

Conclusions

This is the first study demonstrating that peripheral blood monocyte count increased following thoracic surgery in patients with ILDs while values decreased again over time. High postoperative monocyte count was associated with worse post-operative clinical and functional outcomes. On the contrary, RDW did not seem to be a reliable biomarker for patients undergoing thoracic surgery, while its values increased over time. High postoperative monocyte count could be a negative prognostic indicator for patients with ILDs undergoing thoracic surgeries and highlight the need for meticulous evaluation of specific individuals towards a precision medicine risk stratification approach. Larger prospective studies are needed to validate if peripheral blood monocyte count can become a useful prognostic biomarker for these patients.

Conflict of Interest

None to declare.

Funding

The publication fees of this manuscript have been financed by the Research Council of the University of Patras.

Data Availability

Data are available upon request from the corresponding author.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation E6 guidelines for Good Clinical Practice and the local regulations. Retrospective data collection and analysis was approved by the Institutional Review Board and theLocal Ethics Committee of Panagia i Voitheia (protocol number: 23322/24-11-16, 27448/22-11-19).

Authors' Contribution

TK and AT designed the study. TK, TM, PT, MK, EK, KV, EM, EZ, GT, VG, VS, EK, ET, DK, GH, VT, AG, KK, PB, IV, FS, NK, DB and AT were involved in methodology and data collection. TK, TM, and AT were involved in data analysis and wrote the first version of the manuscript. AT supervised the project. TK and TM contributed equally to this work. All authors reviewed the manuscript. All authors offered intellectual contributions and approved the final form of the manuscript.

Informed Consent

Written informed consent was obtained from each patient before the surgical procedure.

References

1) McCarthy C, Keane MP. Contemporary Concise Review 2021: Interstitial lung disease. Respirology 2022; 27: 539-548.
2) Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, Behr J, Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez FJ, Myers J, Protzko S, Raghu G, Richeldi L, Sverzellati N, Swigris J, Valeyre D. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013; 188: 733-748.
3) Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, Kreuter M, Lynch DA, Maher TM, Martinez FJ, Molina-Molina M, Myers JL, Nicholson AG, Ryerson CJ, Strek ME, Troy LK, Wijsenbeek M, Mammen MJ, Hossain T, Bissell BD, Herman DD, Hon SM, Kheir F, Khor YH, Macrea M, Antoniou KM, Bouros D, Buendia-Roldan I, Caro F, Crestani B, Ho L, Morisset J, Olson AL, Podolanczuk A, Poletti V, Selman M, Ewing T, Jones S, Knight SL, Ghazipura M, Wilson KC. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022; 205: e18-e47.
4) Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. N Engl J Med 2020; 383: 958-968.
5) Tzouvelekis A, Karampitsakos T, Kourtidou S, Bouros E, Tzilas V, Katsaras M, Antonou C, Dassiou M, Bouros D. Impact of Depression on Patients With Idiopathic Pulmonary Fibrosis. Front Med (Lausanne) 2020; 7: 29.
6) Wijsenbeek M, Suzuki A, Maher TM. Interstitial lung diseases. Lancet 2022; 400: 769-786.
7) Meyer KC. Diagnosis and management of interstitial lung disease. Transl Respir Med 2014; 2: 4.
8) Kreider ME, Hansen-Flaschen J, Ahmad NN, Rossman MD, Kaiser LR, Kucharczuk JC, Shrager JB. Complications of video-assisted thoracoscopic lung biopsy in patients with interstitial lung disease. Ann Thorac Surg 2007; 83: 1140-1144.
9) Samhouri BF, Kanj AN, Chehab O, Ryu JH. Outcomes for Elective Open and Thoracoscopic Surgical Lung Biopsies in the United States and Temporal Trends. Mayo Clin Proc Innov Qual Outcomes 2022; 6: 87-97.
10) Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-Hospital Mortality after Surgical Lung Biopsy for Interstitial Lung Disease in the United States. 2000 to 2011. Am J Respir Crit Care Med 2016; 193: 1161-1167.
11) Rotolo N, Imperatori A, Dominioni L, Facchini A, Conti V, Castiglioni M, Spanevello A. Efficacy and safety of surgical lung biopsy for interstitial disease. Experience of 161 consecutive patients from a single institution in Italy. Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 251-258.
12) Karampitsakos T, Torrisi S, Antoniou K, Manali E, Korbila I, Papaioannou O, Sampsonas F, Katsaras M, Vasarmidi E, Papakosta D, Domvri K, Fouka E, Organtzis I, Daniil Z, Dimeas I, Kirgou P, Gourgoulianis KI, Papanikolaou IC, Markopoulou K, Kounti G, Tsapakidou E, Papadopoulou E, Tatsis K, Gogali A, Kostikas K, Tzilas V, Chrysikos S, Papiris S, Bouros D, Kreuter M, Tzouvelekis A. Increased monocyte count and red cell distribution width as prognostic biomarkers in patients with Idiopathic Pulmonary Fibrosis. Respir Res 2021; 22: 140.
13) Scott MKD, Quinn K, Li Q, Carroll R, Warsinske H, Vallania F, Chen S, Carns MA, Aren K, Sun J, Koloms K, Lee J, Baral J, Kropski J, Zhao H, Herzog E, Martinez FJ, Moore BB, Hinchcliff M, Denny J, Kaminski N, Herazo-Maya JD, Shah NH, Khatri P. Increased monocyte count as a cellular biomarker for poor outcomes in fibrotic diseases: a retrospective, multicentre cohort study. The Lancet Respir Med 2019; 7: 497-508.
14) Kreuter M, Lee JS, Tzouvelekis A, Oldham JM, Molyneaux PL, Weycker D, Atwood M, Kirchgaessler KU, Maher TM. Monocyte Count as a Prognostic Biomarker in Patients with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2021; 204: 74-81.
15) Perrot CY, Karampitsakos T, Herazo-Maya JD. Monocytes and macrophages: emerging mechanisms and novel therapeutic targets in pulmonary fibrosis. Am J Physiol Cell Physiol 2023; 325: C1046-c1057.

16) Saku A, Fujisawa T, Nishimoto K, Yoshimura K, Hozumi H, Karayama M, Suzuki Y, Furuhashi K, Enomoto N, Nakamura Y, Inui N, Suda T. Prognostic significance of peripheral blood monocyte and neutrophil counts in rheumatoid arthritis-associated interstitial lung disease. Respir Med 2021; 182: 106420.

17) Karampitsakos T, Akinosoglou K, Papaioannou O, Panou V, Koromilias A, Bakakos P, Loukides S, Bouros D, Gogos C, Tzouvelekis A. Increased Red Cell Distribution Width Is Associated With Disease Severity in Hospitalized Adults With SARS-CoV-2 Infection: An Observational Multicentric Study. Front Med (Lausanne) 2020; 7: 616292.

18) Karampitsakos T, Dimakou K, Papaioannou O, Chrysikos S, Kaponi M, Bouros D, Tzouvelekis A, Hillas G. The role of increased red cell distribution width as a negative prognostic marker in patients with COPD. Pulm Pharmacol Ther 2020; 60: 101877.

19) Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, Kreuter M, Lynch DA, Maher TM, Martinez FJ, Molina-Molina M, Myers JL, Nicholson AG, Ryerson CJ, Strek ME, Troy LK, Wijsenbeek M, Mammen MJ, Hossain T, Bissell BD, Herman DD, Hon SM, Kheir F, Khor YH, Macrea M, Antoniou KM, Bouros D, Buendia-Roldan I, Caro F, Crestani B, Ho L, Morisset J, Olson AL, Podolanczuk A, Poletti V, Selman M, Ewing T, Jones S, Knight SL, Ghazipura M, Wilson KC. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022; 205: e18-e47.

20) Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, Behr J, Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez FJ, Myers J, Protzko S, Raghu G, Richeldi L, Sverzellati N, Swigris J, Valeyre D, Pneumonias AECoII. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013; 188: 733-748.

21) Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collard HR, Duggal A, Galvin L, Inoue Y, Jenkins RG, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendía-Roldán I, Selman M, Travis WD, Walsh S, Wilson KC. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018; 198: e44-e68.

22) Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, Bargagli E, Chung JH, Collins BF, Bendstrup E, Chami HA, Chua AT, Corte TJ, Dalphin JC, Danoff SK, Diaz-Mendoza J, Duggal A, Egashira R, Ewing T, Gulati M, Inoue Y, Jenkins AR, Johannson KA, Johkoh T, Tamae-Kakazu M, Kitaichi M, Knight SL, Koschel D, Lederer DJ, Mageto Y, Maier LA, Matiz C, Morell F, Nicholson AG, Patolia S, Pereira CA, Renzoni EA, Salisbury ML, Selman M, Walsh SLF, Wuyts WA, Wilson KC. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2020; 202: e36-e69.

23) Feray S, Lubach J, Joshi GP, Bonnet F, Van de Velde M. PROSPECT guidelines for video-assisted thoracoscopic surgery: a systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia 2022; 77: 311-325.

24) Sato T, Kondo H, Watanabe A, Nakajima J, Niwa H, Horio H, Okami J, Okumura N, Sugio K, Teramukai S, Kishi K, Ebina M, Sugiyama Y, Kondo T, Date H. A simple risk scoring system for predicting acute exacerbation of interstitial pneumonia after pulmonary resection in lung cancer patients. Gen Thorac Cardiovasc Surg 2015; 63: 164-172.

25) Sato T, Teramukai S, Kondo H, Watanabe A, Ebina M, Kishi K, Fujii Y, Mitsudomi T, Yoshimura M, Maniwa T, Suzuki K, Kataoka K, Sugiyama Y, Kondo T, Date H, Japanese Association for Chest S. Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer. J Thorac Cardiovasc Surg 2014; 147: 1604-1611 e1603.

26) Teoh AKY, Jo HE, Chambers DC, Symons K, Walters EH, Goh NS, Glaspole I, Cooper W, Reynolds P, Moodley Y, Corte TJ. Blood monocyte counts as a potential prognostic marker for IPF: Analysis from the Australian IPF registry. Eur Respir J 2020: 1901855.

27) Nathan SD, Reffett T, Brown AW, Fischer CP, Shlobin OA, Ahmad S, Weir N, Sheridan MJ. The red cell distribution width as a prognostic indicator in idiopathic pulmonary fibrosis. Chest 2013; 143: 1692-1698.

28) Kawamura K, Ichikado K, Anan K, Yasuda Y, Sekido Y, Suga M, Ichiyasu H, Sakagami T. Monocyte count and the risk for acute exacerbation of fibrosing interstitial lung disease: A retrospective cohort study. Chron Respir Dis 2020; 17: 1479973120909840.

29) Balci A, Düz ME, Vurmaz A, Çilekar Ş, Kaya F. Comprehensive biomarker analysis of patients with idiopathic pulmonary fibrosis and interstitial lung disease with healthy individuals. Eur Rev Med Pharmacol Sci 2023; 27: 5468-5479.

30) Fibla JJ, Brunelli A, Cassivi SD, Deschamps C. Aggregate risk score for predicting mortality after surgical biopsy for interstitial lung disease†. Interact Cardiovasc Thorac Surg 2012; 15: 276-279.

31) Park JH, Kim DK, Kim DS, Koh Y, Lee S-D, Kim WS, Kim WD, Park SI. Mortality and risk factors for surgical lung biopsy in patients with idiopathic interstitial pneumonia. Eur J Cardiothorac Surg 2007; 31: 1115-1119.

32) Karampitsakos T, Tzouvelekis A, Chrysikos S, Bouros D, Tsangaris I, Fares WH. Pulmonary hypertension in patients with interstitial lung disease. Pulm Pharmacol Ther 2018; 50: 38-46.

33) Karampitsakos T, Papaioannou O, Katsaras M, Sampsonas F, Tzouvelekis A. Interstitial Lung Diseases and the Impact of Gender. Clin Chest Med 2021; 42: 531-541.

34) Pastre J, Khandhar S, Barnett S, Ksovreli I, Mani H, Brown AW, Shlobin OA, Ahmad K, Khangoora V, Aryal S, Morris DL, King CS, Nathan SD. Surgical Lung Biopsy for Interstitial Lung Disease. Safety and Feasibility at a Tertiary Referral Center. Ann Am Thorac Soc 2021; 18: 460-467.

35) Iwata T, Yoshida S, Fujiwara T, Wada H, Nakajima T, Suzuki H, Yoshino I. Effect of Perioperative Pirfenidone Treatment in Lung Cancer Patients With Idiopathic Pulmonary Fibrosis. Ann Thorac Surg 2016; 102: 1905-1910.

36) Karampitsakos T, Spagnolo P, Mogulkoc N, Wuyts WA, Tomassetti S, Bendstrup E, Molina-Molina M, Manali ED, Unat Ö S, Bonella F, Kahn N, Kolilekas L, Rosi E, Gori L, Ravaglia C, Poletti V, Daniil Z, Prior TS, Papanikolaou IC, Aso S, Tryfon S, Papakosta D, Tzilas V, Balestro E, Papiris S, Antoniou K, Bouros D, Wells A, Kreuter M, Tzouvelekis A. Lung cancer in patients with idiopathic pulmonary fibrosis: A retrospective multicentre study in Europe. Respirology 2023; 28: 56-65.

37) Hao X, Hao J, Chen C, Peng H, Zhang J, Cao Q, Liu L. Risk factors for acute exacerbation of interstitial lung disease following lung cancer resection: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg 2022; 34: 744-752.

38) Tzouvelekis A, Antoniou K, Kreuter M, Evison M, Blum TG, Poletti V, Grigoriu B, Vancheri C, Spagnolo P, Karampitsakos T, Bonella F, Wells A, Raghu G, Molina-Molina M, Culver DA, Bendstrup E, Mogulkoc N, Elia S, Cadranel J, Bouros D. The DIAMORFOSIS (DIAgnosis and Management Of lung canceR and FibrOSIS) survey: international survey and call for consensus. ERJ Open Res 2021; 7.

39) Herazo-Maya JD, Sun J, Molyneaux PL, Li Q, Villalba JA, Tzouvelekis A, Lynn H, Juan-Guardela BM, Risquez C, Osorio JC, Yan X, Michel G, Aurelien N, Lindell KO, Klesen MJ, Moffatt MF, Cookson WO, Zhang Y, Garcia JGN, Noth I, Prasse A, Bar-Joseph Z, Gibson KF, Zhao H, Herzog EL, Rosas IO, Maher TM, Kaminski N. Validation of a 52-gene risk profile for outcome prediction in patients with idiopathic pulmonary fibrosis: an international, multicentre, cohort study. Lancet Respir Med 2017; 5: 857-868.

40) Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. N Engl J Med 2018; 378: 1811-1823.

41) Betensley A, Sharif R, Karamichos D. A systematic review of the role of dysfunctional wound healing in the pathogenesis and treatment of idiopathic pulmonary fibrosis. J Clin Med 2016; 6: E2.

42) Yu G, Tzouvelekis A, Wang R, Herazo-Maya JD, Ibarra GH, Srivastava A, de Castro JPW, Deluliis G, Ahangari F, Woolard T, Aurelien N, Arrojo EDR, Gan Y, Graham M, Liu X, Homer RJ, Scanlan TS, Mannam P, Lee PJ, Herzog EL, Bianco AC, Kaminski N. Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function. Nat Med 2018; 24: 39-49.

43) Allden SJ, Ogger PP, Ghai P, McErlean P, Hewitt R, Toshner R, Walker SA, Saunders P, Kingston S, Molyneaux PL, Maher TM, Lloyd CM, Byrne AJ. The Transferrin Receptor CD71 Delineates Functionally Distinct Airway Macrophage Subsets during Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2019; 200: 209-219.

44) Heukels P, van Hulst JAC, van Nimwegen M, Boorsma CE, Melgert BN, van den Toorn LM, Boomars KAT, Wijsenbeek MS, Hoogsteden H, von der Thusen JH, Hendriks RW, Kool M, van den Blink B. Fibrocytes are increased in lung and peripheral blood of patients with idiopathic pulmonary fibrosis. Respir Res 2018; 19: 90.

45) Karampitsakos T, Galaris A, Chrysikos S, Papaioannou O, Vamvakaris I, Barbayianni I, Kanellopoulou P, Grammenoudi S, Anagnostopoulos N, Stratakos G, Katsaras M, Sampsonas F, Dimakou K, Manali ED, Papiris S, Tourki B, Juan-Guardela BM, Bakakos P, Bouros D, Herazo-Maya JD, Aidinis V, Tzouvelekis A. Expression of PD-1/PD-L1 axis in mediastinal lymph nodes and lung tissue of human and experimental lung fibrosis indicates a potential therapeutic target for idiopathic pulmonary fibrosis. Respir Res 2023; 24: 279.

46) Ntatsoulis K, Karampitsakos T, Tsitoura E, Stylianaki EA, Matralis AN, Tzouvelekis A, Antoniou K, Aidinis V. Commonalities Between ARDS, Pulmonary Fibrosis and COVID-19: The Potential of Autotaxin as a Therapeutic Target. Front Immunol 2021; 12: 687397.

47) Xylourgidis N, Min K, Ahangari F, Yu G, Herazo-Maya JD, Karampitsakos T, Aidinis V, Binzenhöfer L, Bouros D, Bennett AM, Kaminski N, Tzouvelekis A. Role of dual-specificity protein phosphatase DUSP10/MKP-5 in pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol 2019; 317: L678-l689.

48) Nouno T, Okamoto M, Ohnishi K, Kaieda S, Tominaga M, Zaizen Y, Ichiki M, Momosaki S, Nakamura M, Fujimoto K, Fukuoka J, Shimizu S, Komohara Y, Hoshino T. Elevation of pulmonary CD163(+) and CD204(+) macrophages is associated with the clinical course of idiopathic pulmonary fibrosis patients. J Thorac Dis 2019; 11: 4005-4017.

49) Moeller A, Gilpin SE, Ask K, Cox G, Cook D, Gauldie J, Margetts PJ, Farkas L, Dobranowski J, Boylan C, O'Byrne PM, Strieter RM, Kolb M. Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2009; 179: 588-594.

50) Evren E, Ringqvist E, Tripathi KP, Sleiers N, Rives IC, Alisjahbana A, Gao Y, Sarhan D, Halle T,

Sorini C, Lepzien R, Marquardt N, Michaelsson J, Smed-Sorensen A, Botling J, Karlsson MCI, Villablanca EJ, Willinger T. Distinct developmental pathways from blood monocytes generate human lung macrophage diversity. Immunity 2021; 54: 259-275.e7.

51) Aran D, Looney AP, Liu L, Wu E, Fong V, Hsu A, Chak S, Naikawadi RP, Wolters PJ, Abate AR, Butte AJ. Reference-based analysis of lung single-cell sequencing reveals a transitional profibrotic macrophage. Nat Immunol 2019; 20: 163-172.

52) Greiffo FR, Viteri-Alvarez V, Frankenberger M, Dietel D, Ortega-Gomez A, Lee JS, Hilgendorff A. CX3CR1-fractalkine axis drives kinetic changes of monocytes in fibrotic interstitial lung diseases. Eur Respir J 2020; 55.

53) Prasse A, Probst C, Bargagli E, Zissel G, Toews GB, Flaherty KR, Olschewski M, Rottoli P, Muller-Quernheim J. Serum CC-chemokine ligand 18 concentration predicts outcome in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2009; 179: 717-723.

54) Epstein D, Nasser R, Mashiach T, Azzam ZS, Berger G. Increased red cell distribution width: A novel predictor of adverse outcome in patients hospitalized due to acute exacerbation of chronic obstructive pulmonary disease. Respir Med 2018; 136: 1-7.

55) Foy BH, Carlson JCT, Reinertsen E, Padros I. Valls R, Pallares Lopez R, Palanques-Tost E, Mow C, Westover MB, Aguirre AD, Higgins JM. Association of Red Blood Cell Distribution Width With Mortality Risk in Hospitalized Adults With SARS-CoV-2 Infection. JAMA Netw Open 2020; 3: e2022058-e2022058.

56) Karampitsakos T, Papaioannou O, Tsiri P, Katsaras M, Katsimpris A, Kalogeropoulos AP, Malakounidou E, Zarkadi E, Tsirikos G, Georgiopoulou V, Sotiropoulou V, Koulousousa E, Chourpiliadi C, Matsioulas A, Lagadinou M, Sampsonas F, Akinosoglou K, Marangos M, Tzouvelekis A. Tocilizumab versus baricitinib in hospitalized patients with severe COVID-19: an open label, randomized controlled trial. Clin Microbiol Infect 2023; 29: 372-378.

57) Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 2015; 52: 86-105.

58) Ycas JW, Horrow JC, Horne BD. Persistent increase in red cell size distribution width after acute diseases: A biomarker of hypoxemia? Clin Chim Acta 2015; 448: 107-117.

59) Karampitsakos T, Juan-Guardela BM, Tzouvelekis A, Herazo-Maya JD. Precision medicine advances in idiopathic pulmonary fibrosis. EBioMedicine 2023; 95: 104766.