




# BMJ Open Association of complete blood count parameters with the risk of incident pulmonary heart disease in pneumoconiosis: a retrospective cohort study

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## ABSTRACT

**Background** Pneumoconiosis mostly combines pulmonary and cardiovascular diseases, among which pulmonary heart disease (PHD) is of major concern due to its significant impact on the survival of pneumoconiosis patients. White cell count (WCC), red cell distribution width (RDW) and platelet parameters are thought to affect inflammatory responses and may be predictors of various cardiovascular diseases. However, very few studies have focused on PHD.

**Objectives** To examine the relationship between baseline complete blood count parameters (WCC, RDW, platelet parameters) and the risk of incident PHD in pneumoconiosis patients.

**Design** A retrospective cohort study.

**Setting** This was a single-centre, retrospective cohort study that used data from an Occupational Disease Hospital, Chengdu, Sichuan.

**Participants** A total of 946 pneumoconiosis patients from January 2012 to November 2021 were included in the study. Female patients and patients who had PHD, coronary heart disease, hypertensive heart disease, cardiomyopathy, heart failure, oncological disease, multiple organ dysfunction, AIDS at baseline and follow-up time of less than 6 months were also excluded.

**Outcome measures** We identified PHD according to the patient's discharge diagnosis. We constructed Cox proportional hazard regression models to assess the HR of incident PHD in pneumoconiosis, as well as 95% CIs.

**Results** In the multiple Cox proportional hazard regression analysis, platelet count (PLT) and plateletcrit (PCT) above the median at baseline were associated with an increased risk of PHD in pneumoconiosis with adjusted HR of 1.52 (95% CI 1.09 to 2.12) and 1.42 (95% CI 1.02 to 1.99), respectively.

**Conclusion** Higher baseline PLT and PCT are associated with a higher risk of PHD in pneumoconiosis.

## INTRODUCTION

Pneumoconiosis is a fibrotic respiratory disease caused by the inhalation and deposition of mineral dust in the lungs.<sup>1</sup> Although the worldwide prevalence of pneumoconiosis

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first cohort study to examine the relationship between baseline white cell count, red distribution width, and platelet parameters and the incident pulmonary heart disease in pneumoconiosis patients.
- ⇒ The strengths are the larger sample sizes, the long follow-up and that we controlled for key variables such as dust exposure time, pneumoconiosis stage and comorbidity.
- ⇒ As the study population consisted entirely of male inpatients, caution needs to be taken when applying findings to other populations.
- ⇒ Since the retrospective nature of the analysis, patient's blood samples were not measured on the same machine and measurement error could not be controlled.

has shown a downward trend since 2015, in recent years, the high demand for artificial stone processing, denim jeans manufacturing and other occupations has led to a significant emergence of pneumoconiosis around the world.<sup>2 3</sup> According to the Global Burden of Disease studies, more than 199 000 new patients were reported globally in 2019. Pneumoconiosis was responsible for 479 000 years of life lost and 440 000 years lived with disability in 2019.<sup>4</sup> Therefore, it remains a severe global public health issue.

Previous studies have pointed out that pneumoconiosis increases the morbidity and mortality of pulmonary heart disease (PHD).<sup>5–8</sup> A study found that PHD was diagnosed 17 times more frequently than expected in pneumoconiosis than among other men admitted to the hospital.<sup>9</sup>

Silica may promote injury to the pulmonary vascular system through mechanisms

involving inflammation, endothelial dysfunction and vascular remodelling. Animal experiments revealed elevated expression of proinflammatory and profibrotic genes (TNF- $\alpha$ , MMP-2, TIMP-1, collagen type I, ferroptosis suppressor protein 1) in mice exposed to silica while the expression of endothelium-specific genes (pecan 1, platelet factor 4, nestin) was downregulated.<sup>10–11</sup> These changes in gene expression together led to increased infiltration of inflammatory cells around periarterial, fibrotic inflammatory nodule and collagen deposition. Inflammatory cells or inflammatory granulation tissue can invade the vascular wall, causing splitting and thickening of the elastic fibre layer, hyaline degeneration of the vascular wall, luminal stenosis, or even occlusion, and progressive medial thickening of the small pulmonary arteries as well as muscularisation. Pulmonary emphysema can lead to the extrusion and destruction of capillaries accompanying the alveoli, thus causing a large reduction in pulmonary capillaries, resulting in the disorder of ventilation and blood flow and hypoxia. Hypoxia, in turn, increases the expression of MMP-2, TIMP-1, TIMP-2 and  $\alpha$ -smooth muscle actin genes in adventitial fibroblasts, promoting neointimal hyperplasia. As the degree of fibrosis and emphysema increases, the remodelling range of pulmonary arterioles gradually expands, almost all the vessels of different diameters are involved, and the pulmonary artery pressure increases gradually. This subsequently led to hypertrophy and dilatation of the right ventricle.

A growing body of evidence suggests the great significance of inflammatory processes in the involvement of multiple cardiovascular events. White cell count (WCC), red cell distribution width (RDW) and platelet parameters are thought to affect inflammatory responses and may be predictors of various cardiovascular diseases,<sup>12–17</sup> including atherosclerosis, coronary heart disease, stroke, pulmonary hypertension, myocardial infarction and heart failure. However, very few studies examined the association of complete blood count parameters with the risk of incident PHD. Only one study explored the association of complete blood count parameters with PHD in a COPD population, researchers found that mean platelet volume (MPV) and RDW-standard deviation were correlated with the severity of PHD, and the combination of these two parameters may accurately predict PHD.<sup>15</sup> However, the sample size of the study was small. Usually, long-term pulmonary hypertension causes PHD. According to the European Society of Cardiology/European Respiratory Society Guidelines, pulmonary hypertension is classified into five groups. Previous studies on complete blood count parameters and the incident or prognosis of pulmonary hypertension almost focused on the idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension populations, whereas pulmonary hypertension secondary to pneumoconiosis belongs to group (3), lung disease and/or hypoxia-associated pulmonary hypertension. Therefore, these studies do not provide reliable evidence for the risk of incident PHD in pneumoconiosis. Given the

lack of evidence for the association between complete blood count parameters and the risk of incident PHD in pneumoconiosis, this study intended to establish a retrospective cohort using medical records of pneumoconiosis patients and investigate this unanswered clinical gap.

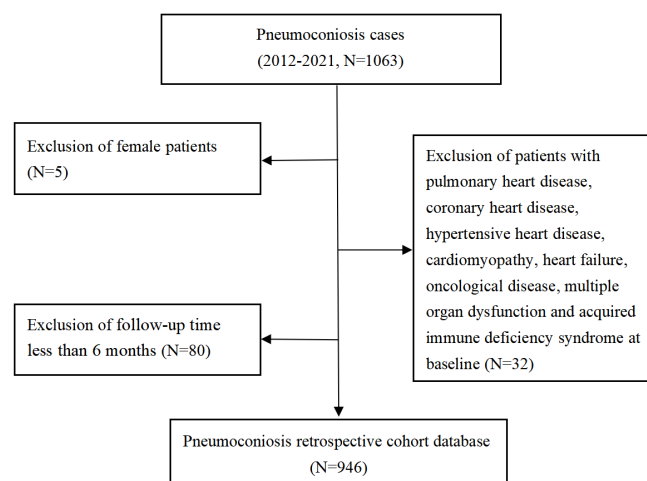
## MATERIALS AND METHODS

### Data source

The study participants were from a hospital-based retrospective cohort. Medical records used in this study were obtained from the West China Fourth Hospital of Sichuan University from January 2012 to November 2021. Definition of diseases according to the International Classification of Diseases-10th Revision (ICD-10) codes. The baseline was the date of patients' first admission between January 2012 and November 2021 on which a blood sample was collected. We collected circulating blood cell parameters on the day of admission including WCC, RDW, PLT, MPV, platelet distribution width (PDW) and plateletcrit (PCT). Follow-up time calculation: from baseline to the date when the patient was first diagnosed with PHD or from baseline to the date of the patients' last discharge during the study. Baseline demographics and comorbidities were recorded.

### Study cohorts

All inpatients with a clinical or occupational diagnosis of pneumoconiosis (J60–J65) and two or more hospitalisations were included in the pneumoconiosis cohort. Clinical diagnosis of pneumoconiosis is defined as a patient who has not yet been diagnosed with pneumoconiosis according to legal and regulatory procedures but has manifestations of interstitial pulmonary fibrosis (J84.101–J84.108) and a history of productive mineral dust exposure. Clinical diagnosis of pneumoconiosis was confirmed by manual medical records review. Female patients were excluded from the study because less than 1% of patients were female. Patients who had PHD (I27.901, I27.902), coronary heart disease (I25.101,



**Figure 1** Flow chart of the participant's selection.

**Table 1** The distributions of baseline characteristics for the study participants stratified by the PHD status

Characteristics at baseline	Mean±SD or N (%) or median (P <sub>25</sub> , P <sub>75</sub> )		t/Z/χ <sup>2</sup>	P value
	No-PHD (N=793)	PHD (N=153)		
Age (years)	49.0±10.0	54.2±12.7	-4.810	<0.001
BMI (kg/m <sup>2</sup> )	23.0±3.2	21.1±3.5	6.860	<0.001
Ethnic			2.305	0.129
Han	697 (87.9)	141 (92.2)		
Non-han	96 (12.1)	12 (7.8)		
Smoking status			10.243	0.006
Never	110 (13.9)	25 (16.3)		
Former	485 (61.1)	108 (70.6)		
Current	198 (25.0)	20 (13.1)		
Dust exposure time (years)	8 (5, 12)	10(6, 20)	3.366	<0.001
Pneumoconiosis stage			37.850	<0.001
Stage I	230 (29.0)	27 (17.6)		
Stage II	227 (28.6)	20 (13.1)		
Stage III	336 (42.4)	106 (69.3)		
COPD	36 (4.5)	10 (6.5)	1.105	0.293
Tuberculosis	72 (9.1)	20 (13.1)	2.329	0.127
Hypertension	55 (6.9)	10 (6.5)	0.032	0.858
WCC (×10 <sup>9</sup> /L, n=939)			1.224	0.269
≤6.4	401 (50.9)	70 (46.1)		
>6.4	386 (49.1)	82 (53.9)		
RDW (% , n=917)			11.575	<0.001
≤13.3	426 (55.5)	60 (40.3)		
>13.3	342 (44.5)	89 (59.7)		
PLT (×10 <sup>9</sup> /L, n=923)			0.026	0.872
≤181	390 (50.4)	74 (49.7)		
>181	384 (49.6)	75 (50.3)		
MPV (fL, n=879)			0.051	0.822
≤10.8	373 (50.7)	71 (49.7)		
>10.8	363 (49.3)	72 (50.3)		
PDW (fL, n=879)			0.012	0.912
≤15.0	372 (50.5)	73 (51.1)		
>15.0	364 (49.5)	70 (48.9)		
PCT (% , n=878)			0.073	0.787
≤0.2	403 (54.8)	76 (53.5)		
>0.2	333 (45.2)	66 (46.5)		

BMI, body mass index; COPD, chronic obstructive pulmonary disease; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; PHD, pulmonary heart disease; PLT, platelet count; RDW, red cell distribution width; WCC, white cell count.

I49.902), hypertensive heart disease (I11, I13), cardiomyopathy (I42), heart failure (I50), oncological disease (C00-C97), multiple organ dysfunction, AIDS (B24) at baseline and follow-up time of less than 6 months were also excluded (figure 1). There is not a clear ICD-10 code for multiple organ dysfunction so terminology query was used to identify patients with multiple organ dysfunction.

## Outcome

In this study, the determination of PHD (I27.901, I27.902) was based on the discharge diagnosis.

## Covariates

Age, body mass index (BMI), ethnic, smoking status, dust exposure time, pneumoconiosis stage and comorbidities were obtained from the medical records. Pneumoconiosis

**Table 2** The association of complete blood count parameters and PHD in pneumoconiosis

Parameters	Crude HR (95% CI)	Model I HR (95% CI)	Model II HR (95% CI)
WCC ( $\times 10^9/L$ )			
≤6.4	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>6.4	1.32 (0.96 to 1.82)	1.22 (0.89 to 1.69)	1.21 (0.87 to 1.67)
RDW (%)			
≤13.3	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>13.3	1.83 (1.31 to 2.54)	1.31 (0.93 to 1.85)	1.30 (0.92 to 1.84)
PLT ( $\times 10^9/L$ )			
≤181	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>181	1.29 (0.94 to 1.78)	1.52 (1.09 to 2.12)	1.49 (1.06 to 2.08)
MPV (fL)			
≤10.8	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>10.8	0.96 (0.69 to 1.34)	1.10 (0.79 to 1.54)	1.10 (0.79 to 1.54)
PDW (fL)			
≤15.0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>15.0	1.48 (1.06 to 2.06)	1.27 (0.90 to 1.78)	1.23 (0.87 to 1.74)
PCT (%)			
≤0.2	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>0.2	1.33 (0.95 to 1.85)	1.42 (1.02 to 1.99)	1.40 (1.00 to 1.96)

Model I: Adjusted for age, body mass index, ethnic, smoking status, dust exposure time, pneumoconiosis stage.  
 Model II: Model I with additional adjustment for chronic obstructive pulmonary disease, tuberculosis and hypertension.  
 MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; PHD, pulmonary heart disease; PLT, platelet count; RDW, red cell distribution width; WCC, white cell count.

is classified into stages I, II and III according to the diagnostic criteria for occupational pneumoconiosis (GBZ 70–2009/GBZ 70–2015).<sup>18 19</sup> Three related comorbidities were selected for adjustment, including chronic obstructive pulmonary disease (J44.000, J44.100, J44.101), tuberculosis (A15–A19) and hypertension (I10, I12, I15).

### Statistical analysis

The quantitative data fitting the normal distribution was represented by mean and SD, otherwise median and quartile were used. Differences in patient characteristics were investigated with Student's t-test or Mann-Whitney U test for continuous variables and  $\chi^2$  test for categorical variables. We constructed Cox proportional hazard regression models to assess the HR of incident PHD in pneumoconiosis, as well as 95% CIs. Standardised Schoenfeld residuals were used to test whether the proportional risk assumption was met. We used SAS V.9.4 for data analysis and R V.4.3.0 for graphics. Two-tailed test was used for all analyses and a p value of less than 0.05 was considered statistically significant.

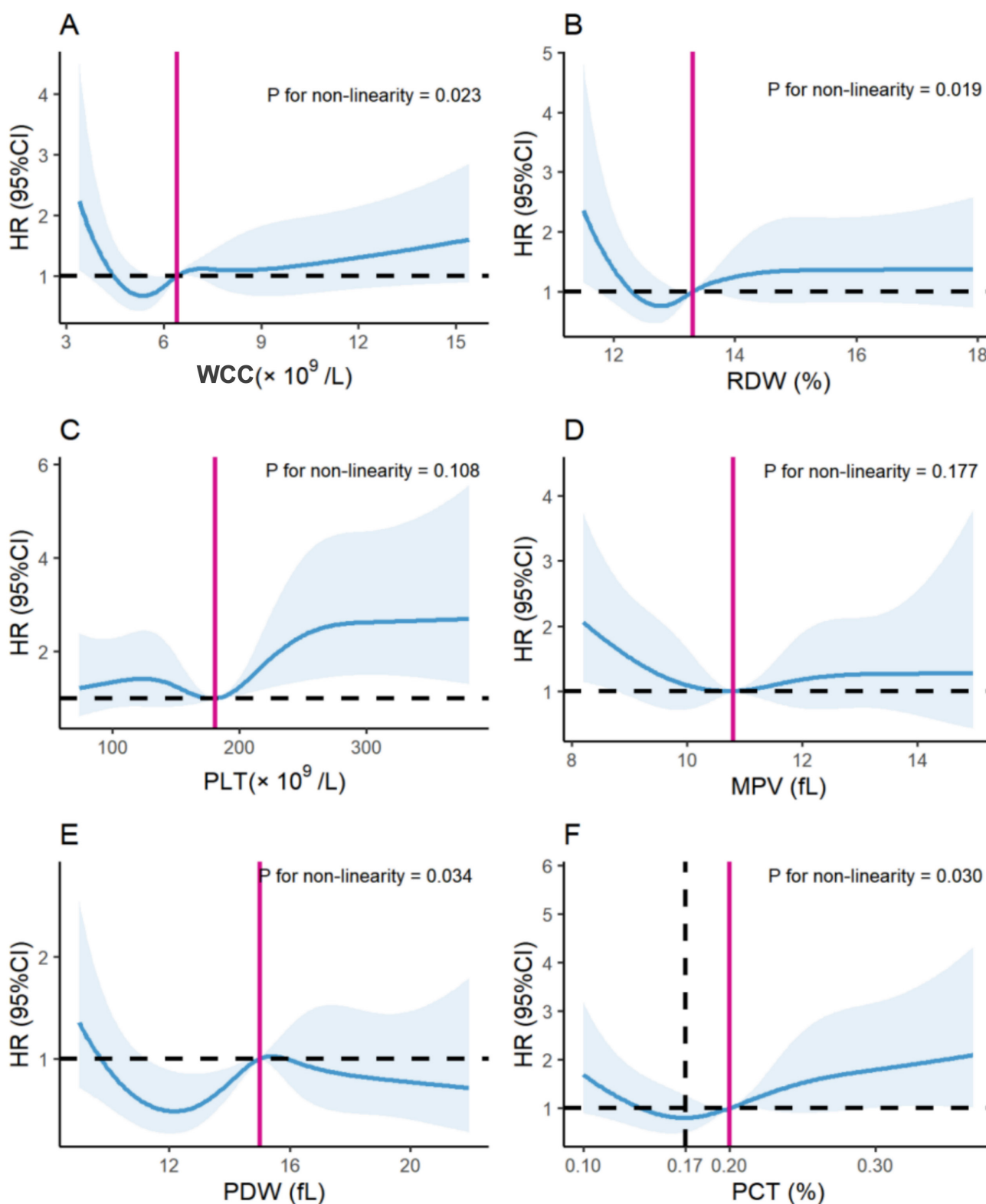
### Patient and public involvement

No patients were actively involved in setting the research question, outcome measures nor involved in the design of the study. Patients were not involved in the recruitment, or conduct, or dissemination plans of this research.

### RESULTS

A total of 946 pneumoconiosis patients were included in the final analysis (table 1). The median follow-up time was 38 (IQ1–IQ3=22–67) months. The mean age was 54.2±12.7 years in the PHD group and 49.0±10.0 years in the no-PHD group. Pneumoconiosis without PHD at the end of the follow-up had a higher BMI compared with those with PHD ( $p<0.001$ ). The median value of dust exposure time was 10 and 8 years in the PHD group and no-PHD group, respectively. Pneumoconiosis with PHD at the end of the follow-up had a longer dust exposure time than those without PHD ( $p<0.001$ ). The distribution of smoking status was different between two groups ( $p<0.05$ ). The never, former, current smoking were 16.3%, 70.6%, 13.1% in PHD group and 13.9%, 61.1%, 25.0% in no-PHD group. The distribution of pneumoconiosis stage was significantly different between PHD group and no-PHD group ( $p<0.001$ ). Stage III accounts for the largest proportion of pneumoconiosis and more than half of the participants were stage III in pneumoconiosis with PHD (68.3%). The proportions of comorbidities in the PHD group and no-PHD group were as follows: COPD (6.5% vs 4.5%); tuberculosis (13.1% vs 9.1%) and hypertension (6.5% vs 6.9%). Biochemical parameters were divided into two categories according to the median. The proportion of categories with above median RDW was higher in the PHD group compared with no-PHD group





**Figure 2** Non-linear associations between complete blood count parameters and risk of incident PHD in pneumoconiosis patients. (A) White cell count and incident PHD. (B) RDW and incident PHD. (C) Platelet count and incident PHD. (D) MPV and incident PHD. (E) Platelet distribution width (PDW) and incident PHD. (F) PCT and incident PHD. HRs are indicated by solid blue lines and 95% CIs by blue-shaded areas. Reference lines for the median of each complete blood count parameters are indicated by solid red lines, with knots placed at 5th, 35th, 50th, 65th and 95th centiles of each complete blood count parameters distribution. All models were adjusted for age, body mass index, ethnic, smoking status, dust exposure time and pneumoconiosis stage. MPV, mean platelet volume; PCT, plateletcrit; PHD, pulmonary heart disease; PLT, platelet; RDW, red cell distribution width; WCC, white cell count.

( $p < 0.001$ ). However, the distributions of WCC, PLT, MPV, PDW and PCT showed no difference in the two groups. During the follow-up period, the cumulative incidence of PHD was 16.2%.

Each complete blood count parameters was included in the Cox proportional hazard regression model separately, the results are shown in table 2. Model I adjusted for age, BMI, ethnic, smoking status, dust exposure time and pneumoconiosis stage. Model II was additionally adjusted for comorbidities. The results of model I and model II were consistent. Patients with PLT above the median ( $>181 \times 10^9/L$ ) at baseline had a 52% higher risk of incident PHD (HR 1.52, 95% CI 1.09 to 2.12) compared with those with PLT below the median ( $\leq 181 \times 10^9/L$ ) in model I. PCT also exhibited a significant positive association with the risk of incident PHD (HR 1.42, 95% CI 1.02 to 1.99). However, we found no association between baseline WCC, RDW, MPV, PCT and the risk of incident PHD in pneumoconiosis ( $p > 0.05$ ). The results of the proportional hazards assumption and the HRs of all covariates from model I and model II are shown in online supplemental files 1 and 2.

In figure 2, we used restricted cubic splines to explore potential non-linear associations of complete blood count parameters with the risk of incident PHD in pneumoconiosis, adjusted for covariates as in model I. The results of the test statistics and p value of the analysis of non-linear associations are in online supplemental file 3. There were non-linear associations between WCC, RDW, PDW, PCT and the risk of incident PHD ( $p < 0.05$ ), and there were no non-linear associations between PLT and MPV and the risk of incident PHD ( $p > 0.05$ ). The risk of incident PHD was relatively flat until around the median of PLT ( $181 \times 10^9/L$ ) and then started to increase afterwards. There was a U-shaped relation between baseline PCT and the risk of incident PHD in pneumoconiosis. When  $PCT < 0.17\%$ , a decreasing trend was showed in the risk of incident PHD as PCT increased, but the HR was insignificant; when  $PCT > 0.17\%$ , the risk of incident PHD in pneumoconiosis started to increase slowly as PCT increased.

## DISCUSSION

To our knowledge, this is the first study to examine complete blood count parameters and PHD in a pneumoconiosis population. Our study demonstrates that after adjusting for age, BMI, ethnic, smoking status, dust exposure time, pneumoconiosis stage and the presence of comorbidities, higher baseline PLT and PCT were associated with higher risk of PHD in pneumoconiosis.

Studies have shown that pulmonary vascular remodeling is due to the altered functional status of WCC rather than the absolute number.<sup>20</sup> Activated leucocytes release a variety of cytokines resulting in endothelial adhesion and endothelial migration of leucocytes and ultimately pulmonary vascular remodeling.<sup>21</sup> This is consistent with our finding that there is no association between WCC and the risk of incident PHD in pneumoconiosis.

RDW reflects the variation in the size of circulating red blood cells, elevated RDW is now considered to be linked with an underlying inflammatory process. A previous study has demonstrated a strong association of RDW with high-sensitivity C reactive protein and erythrocyte sedimentation rate independent of numerous confounding factors.<sup>22</sup> In a case-control study, Yu *et al*<sup>15</sup> observed a 1.4-fold increase in the risk of PHD in patients with COPD for each unit increase in RDW-SD (OR=1.371,  $p < 0.001$ ). However, this study did not state which confounders were adjusted.<sup>15</sup> We found that the association between elevated RDW and the risk of incident PHD in pneumoconiosis was significant in the unadjusted model, but lost statistical significance after adjusting for age and BMI. Therefore, we suggested that there was no association between elevated RDW and the risk of incident PHD in pneumoconiosis.

Platelets are traditionally thought of as passive mediators of coagulation reactions; however, coagulation and inflammation are interrelated and recent work has illustrated the proinflammatory role of platelets. Through interactions with endothelial cells and WCC, platelets participate in inflammatory processes and accelerate cardiovascular disease development.<sup>13 23</sup> A bidirectional Mendelian randomisation study of 15 996 participants demonstrated a positive causal effect of PLT on the risk of hypertension.<sup>24</sup> Higher PLC could be used as a predictor of future cardiac events. Guo *et al* found that plasma PDW and MPV levels were positively correlated with pulmonary artery pressure and cardiac function grade.<sup>25</sup> A study conducted on children has come to a similar conclusion that MPV, PDW and PCT are positively correlated with right ventricular diameter and may be good predictors of prognosis in pulmonary hypertension.<sup>26</sup> A single-centre retrospective cohort study found that higher baseline PLT and PCT, but not MPV, were associated with increased cardiovascular mortality<sup>27</sup> which is similar to our finding. A recent comment has stated that MPV measurements are not standardised and that differences in the time from blood collection to MPV measurement, type of anticoagulant used and measurement equipment may lead to a deviation of 2%–50% in MPV results.<sup>28</sup> This may be the reason why we failed to associate baseline MPV with the risk of incident PHD in pneumoconiosis.

## Strengths and limitations

One of the strengths of this study is the larger sample sizes and longer follow-up times. In addition, we controlled for key variables such as dust exposure time, pneumoconiosis stage and comorbidity. Furthermore, the exclusion of participants with less than 6 months of follow-up helped to avoid reverse causality. However, this study has several limitations. As the study population consisted entirely of male inpatients, caution needs to be taken when applying findings to other populations. Due to the lack of data on leucocyte subtypes, we were not able to analyse the association of each leucocyte subtype with the risk of incident PHD in pneumoconiosis patients. Since the retrospective nature of the study, patient's

blood samples were not measured on the same machine and measurement error could not be controlled, but we thought this also proved the applicability of our results to the whole community. Oral medications may affect the development of PHD, unfortunately, due to data limitations, a lack of adjustment for drug treatment exists.

## Conclusion

In summary, in this retrospective cohort study, we found that higher baseline PLT and PCT were associated with higher risk of PHD in pneumoconiosis. As indicators of routine blood testing, PLT and PCT are obtained without incremental cost or additional blood necessary. In the future, these circulating blood biomarkers, along with other biomarkers, can be used for risk stratification of pneumoconiosis patients and guide clinicians in intervention.

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**Contributors** Conceptualisation: LL and SP. Data curation: LL, SP, YW, WY, LC, YY and QZ. Formal analysis: LL and SP. Investigation: LL, SP, YW, WY, WD and YS. Methodology: LL, SP, JLiiao and DW. Project administration: LL, YY and QZ. Resources: LL, SP, JLiiao, XJ, LP, WD, QH, DW, JS, LC, SH, LZ, YS, JLi, BZ, YY and QZ. Software: LL and SP. Supervision: LL, SP, YY, QZ. Validation: LL and SP. Visualisation: LL, SP, YW and WY. Writing-original draft: LL, SP and QZ. Writing-review and editing: LL, YY and QZ. QZ is the guarantor.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study was approved by the Research Ethics Committee of the West China Fourth Hospital of Sichuan University (HXSJ-EC-2021053). Patient approval and informed consent were waived due to the retrospective nature of this study.

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**Data availability statement** Data are available on reasonable request.

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