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Early View

Research letter

Blood monocyte counts as a potential prognostic marker for IPF: Analysis from the Australian IPF registry

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Blood monocyte counts as a potential prognostic marker for IPF: Analysis from the Australian IPF registry.

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing lung disease that leads to unrelenting dyspnea and chronic cough and ultimately respiratory failure.[1] IPF is characterized by a variable disease course that remains difficult to predict for an individual at diagnosis.[2] In the current era, with the advent of anti-fibrotic therapy which can slow disease progression, it is increasingly important to identify patients with early disease and to target those patients who are at most risk of rapid decline.[3] However, despite multiple studies proposing novel potential prognostic biomarkers, the current ATS/ERS/JRS/ALAT guideline statements dismissed the use of these biomarkers except in a research capacity.[3,4]

Recently, in this Journal, Scott and colleagues[5] have suggested that peripheral blood monocyte count may be a powerful biomarker capable of predicting poorer prognosis amongst IPF patients. In a retrospective analysis using transcriptome microarray data, the investigators found that estimated CD14+ monocyte percentages above the mean were associated with shorter transplant-free survival times. Using a threshold monocyte value of $0{\cdot}95*10^3/\mu L$ or greater, the investigators were able to validate their exploratory analysis using several independent cohorts. Higher absolute CD14+ monocyte counts were found in the COMET cohort in patients who had progressive disease and in those that were classified as high-risk in the Yale cohort. Higher absolute monocyte counts were found to be associated with increased risk of mortality in several other larger validation cohorts. This finding remained significant following adjustment for forced vital capacity (FVC) and the gender, age and physiology (GAP) index in each of the COMET, Stanford and Northwestern cohorts.

We sought to reproduce this finding using data from the Australian IPF Registry (AIPFR). The national AIPFR is investigator-led, prospectively acquired and was established in 2012 with the goal of facilitating research into IPF as well as to provide further insight into the epidemiology and management of IPF in Australia.[6] Baseline routine full blood count tests with cell differentials performed on patients recruited into the Registry were extracted for analysis. A total of 231 patients from three Australian states (New South Wales, Victoria and South Australia) were included.

Clinical data had been prospectively entered into the Registry with a follow up duration of 2·4 (1·3 – 3·3) years. The majority of patients were male (71%) with a mean age of 69·9 ± 8·3 years. Patients were found initially to have mild to moderate disease with a mean FVC of 80·3 ± 22·0 % predicted and a mean DLCO of 48·2 ± 16·8 % predicted. Mean blood monocyte counts were significantly higher in the 75 patients who died compared to the 156 patients who remained alive after the follow-up period, although the difference was clinically small [0·66 (0·5 – 0·9) versus 0·6 (0·4 – 0·7)$*10^3/\mu L$; p=0·006]. Additionally, neutrophil and total leucocyte counts were also significantly higher in the deceased patient cohort. A Cox proportional hazards model was used to evaluate the effect of an elevated serum monocyte count on survival of the IPF registry patients. 22 patients had monocyte counts equal to or greater than the value of $0{\cdot}95*10^9/L$, used in Scott and colleagues' study[5]. The Australian standardized upper limit of normal values for neutrophils and total leucocyte counts were used as threshold values at $7*10^9/L$ and $10*10^9/L$ respectively. There were 44 and 50 patients with neutrophil and total leucocyte counts equal or greater than the threshold values respectively. Univariate analysis for mortality showed that elevated monocyte, neutrophil and total leucocyte counts were associated with decreased survival (*Table 1*). Following a multivariate analysis adjusting for age, gender and baseline FVC% predicted, elevated monocyte count remained a significant predictor for poorer survival (HR 2·36, 95% CI 1·18 – 4·70, p=0·02). However, elevated neutrophil and total leucocyte counts also remained independently associated with poorer outcomes (HR 2.10, 95% CI 1.22 – 3.62, p=0.008 and HR 2.07, 95% CI 1.23 – 3.50, p=0.006, respectively).

The limitation of our study relates to the real-world nature of the Registry, in which peripheral blood sampling was dictated by individual physicians and was not necessarily the patients' true baseline at diagnosis. Additionally, there was limited data on the prescription of anti-fibrotic therapy as these agents were not readily available to the Australian public on subsidized government-funded programs prior to 2016. Despite this, one advantage of our Registry data is the availability of relatively longer follow-up time and mortality data of IPF patients recruited.

Our findings add further validity to the notion that a routinely measured blood cell population may have a potential as a biomarker, with elevated monocyte counts suggesting a worse prognosis in the individual patient presenting with IPF. Both monocytes and neutrophils have been postulated to play a role in the pathogenesis of IPF and have also been shown to correlate with disease progression.[7–9] We echo the commentary by Kreuter and Maher[10] in agreeing that there is a need for further detailed studies to provide better mechanistic insights into the role that monocytes and neutrophils have to play in IPF. Given the consistency of the association across several diverse cohorts, including ours, a crucial next step is to accurately delineate the nature of the monocytosis in poor prognosis IPF.

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	Hazard ratio (HR)	95% CI	p value
Age	1.0	1.0 - 1.1	0.11
Gender	1.1	0.7 - 1.9	0.64
FVC% *	0.7	0.7 - 0.9	<0.0001
DLCO% *	0.6	0.5 - 0.8	<0.0001
Monocytes ¶	3.2	1.4 - 7.4	0.005
High monocytes (≥0.95x10^9/L)	2.4	1.3 - 4.4	0.004
Neutrophils ¶	1.2	1.1 - 1.2	<0.0001
High neutrophils (≥7x10^9/L)	2.5	1.5 - 4.1	<0.0001
Total WCC ¶	1.2	1.1 - 1.2	<0.0001
High total WCC (≥10x10^9/L)	2.6	1.6 - 4.1	<0.0001

Table 1. Univariate cox analysis for mortality. *: every 10% change. ¶: Continuous variable. WCC: white cell count.