Peripheral blood monocyte count and outcomes in patients with interstitial lung disease: a systematic review and meta-analysis

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Systematic review and meta-analysis demonstrate that peripheral blood monocyte counts are associated with increased risk of mortality and disease progression in ILD and ILA, indicating a potential role for blood monocytes as a prognostic biomarker. https://bit.ly/43IGuvC

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Abstract

Background Peripheral blood monocyte counts have been associated with poor outcomes in interstitial lung disease (ILD). However, studies are limited by variable biomarker thresholds, analytic approaches and heterogenous populations. This systematic review and meta-analysis characterised the relationship between monocytes and clinical outcomes in ILD.

Methods Electronic database searches were performed. Two reviewers screened abstracts and extracted data. Pooled estimates (hazard ratios (HRs)) of monocyte count thresholds were calculated for their association with mortality using $\geqslant 0.6\times10^9$ and $>0.9\times10^9$ cells·L^{-1} for unadjusted models and $\geqslant 0.95\times10^9$ cells·L^{-1} for adjusted models, using random effects, with heterogeneity and bias assessed. Disease progression associated with monocytes $>0.9\times10^9$cells·L^{-1} was also calculated.

Results Of 3279 abstracts, 13 were included in the systematic review and eight in the meta-analysis. The pooled unadjusted HR for mortality for monocyte counts $\geqslant 0.6\times10^9$ cells·L^{-1} was 1.71 (95% CI 1.34–2.19, p<0.001, I^2=0%) and for monocyte counts $>0.90\times10^9$ cells·L^{-1} it was 2.44 (95% CI 1.53–3.87, p=0.0002, I^2=52%). The pooled adjusted HR for mortality for monocyte counts $\geqslant 0.95\times10^9$ cells·L^{-1} was 1.93 (95% CI 1.24–3.01, p=0.0038 I^2=69%). The pooled HR for disease progression associated with increased monocyte counts was 1.83 (95% CI 1.40–2.39, p<0.0001, I^2=28%).

Conclusions Peripheral blood monocyte counts were associated with an increased risk of mortality and disease progression in patients with ILD.

Introduction

Interstitial lung diseases (ILDs) represent a large and heterogeneous group of disorders characterised by varying degrees of parenchymal inflammation and/or fibrosis [1, 2]. ILDs are often progressive, associated with significant morbidity and early mortality. There are limited treatment options, no curative therapies to date and lung transplantation is not an option for all patients. Research priorities in ILD include improved understanding of disease pathobiology, risk stratification to inform management and prognostication, and identifying novel and effective therapeutic targets [3].

Clinically available biomarkers to predict those at risk of progression would facilitate risk stratification at the time of diagnosis, identifying patients who may benefit from early treatment or referral to lung transplant. Prognostication is also important for patients, to guide decision making and understanding of disease status. The baseline peripheral blood absolute monocyte count has been associated with outcomes in patients with idiopathic pulmonary fibrosis (IPF) [2, 4]. Absolute monocyte count is a component of the complete blood count, a commonly used and widely available routine laboratory test, making this a potentially and readily accessible and inexpensive biomarker.

Monocytes have been suggested to play an important role in the pathogenesis of fibrotic ILD. Aberrantly activated monocyte levels have been found in IPF patients and circulating monocytes can produce profibrotic matricellular proteins [5, 6] leading to progressive pulmonary fibrosis. Previously, a 52-gene signature predicted higher risk in mortality in patients with IPF and was validated in a prospective cohort study [7]; subsequent statistical deconvolution demonstrated that upregulated genes were expressed in monocytes [4]. More recently, peripheral blood mononuclear cells from IPF patients and controls were profiled using single-cell RNA sequencing with classical monocytes increased in both stable and progressive IPF patients, compared to controls [8]. Interestingly, gene enrichment analysis showed increased pro-inflammatory pathways in stable IPF patients compared to those who progressed [8].

The potential role of monocytes as drivers of fibrogenesis may predict disease prognosis in other types of ILD. Previous studies have further described peripheral blood monocyte counts as a potential prognostic biomarker in patients with fibrotic hypersensitivity pneumonitis (fHP) [9], rheumatoid arthritis (RA) associated ILD [10] and interstitial lung abnormalities (ILAs) [11]. However, these studies are limited by variable biomarker thresholds and methodologies and differing outcome measurements and analytic approaches. Given the potential pathophysiologic overlap between different clinical diagnoses of ILD, the potential role of peripheral blood monocyte counts warrants study across different subtypes of fibrotic ILD.

The objective of this systematic review and meta-analysis was to characterise the association between peripheral blood monocyte counts and the clinical outcomes of death or lung transplantation and disease progression in adult patients with ILD or individuals with ILA.

Methods

This systematic review was conducted in accordance with a pre-specified protocol (PROSPERO registration number: CRD42022376916) and has been reported using PRIMSA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.

Search strategy and study selection

Electronic database searches were conducted in MEDLINE, Embase, SCOPUS and Web of Science from inception to 8 December 2022. Keywords and MESH terms for “interstitial lung disease” and “peripheral blood monocyte count” were applied (supplemental table 1). Studies involving adults ⩾18 years of age diagnosed with ILD were included. Studies of children (aged <18 years old), studies reporting on sarcoidosis or coronavirus disease 2019, review articles, case reports, case series and conference abstracts were excluded. Following searches, two reviewers (B.M. and A.G.O.) independently screened titles and abstracts prior to full-text review. Disagreements regarding the eligibility of studies were resolved by consensus or using a third reviewer (K.A.J.).

Data extraction and risk-of-bias assessment

Data were extracted from publications using a standardised, pre-piloted form and verified by a second reviewer. Variables extracted included study characteristics including design, participant characteristics including age, sex, forced vital capacity (FVC) % predicted, monocyte count data, timing of monocyte count measurement and effect estimates for outcomes of interest. Time-to-event outcomes were ascertained from unadjusted and adjusted hazard ratios (HRs), where reported. Where multiple models were presented, effect estimates were taken from the most adjusted models.

Risk-of-bias assessment was conducted independently by two reviewers using the Newcastle–Ottawa Scale (NOS) for assessing nonrandomised studies in meta-analysis. The NOS tool evaluates the risk of bias across three domains, namely selection, comparability and outcome. All studies were included in the analysis regardless of their risk-of-bias rating.

Statistical analysis

The main outcome of interest was mortality and the secondary outcome was disease progression. Monocyte counts were standardised to cells·L^{-1} for comparison across studies. Given the limited number of studies and varying monocyte counts used by different studies, the HRs for monocyte counts of >0.9×10^9 cells·L^{-1} were pooled for unadjusted models and thresholds ⩾0.95×10^9 cells·L^{-1} were pooled for adjusted models. Additionally, the HRs for monocyte counts of ⩾0.6, >0.67 and 0.6–0.8×10^9 cells·L^{-1} were combined for unadjusted models due to the low number of studies available. The HR for a monocyte count >0.9×10^9 cells·L^{-1} associated with disease progression was also calculated. Pooled HRs were estimated using random-effects meta-analysis through the meta package in RStudio [12]. Unadjusted and adjusted estimates were analysed separately except for the outcome of disease progression, where these

were combined. The I^2 statistic was used to evaluate heterogeneity between studies. Publication bias was assessed through funnel plot analysis. All statistical analyses were performed using RStudio.

Results

Search results

A total of 3279 articles were identified. Following removal of duplicates and title/abstract screening, 28 studies underwent full-text review, with 13 included in the systematic review (supplemental figure 1). Of these 13 studies, three reported outcomes using odds ratios (ORs) and two reported monocyte count as a continuous variable. A total of eight studies reported effect measures that could be pooled and were included in the meta-analysis.

Study characteristics

Studies included in the systematic review reported on patients with IPF (n=7) [2, 4, 13–17], indeterminate usual interstitial pneumonia (UIP) (n=1) [18], ILA (n=2) [11, 19], fHP (n=1) [9], anti-melanoma differentiation-associated gene 5 (MDA5) positive dermatomyositis (DM)-ILD (n=1) [20] and a pooled cohort of fibrotic ILD (n=1) [21] (table 1). Most were retrospective cohort studies (one a *post hoc* analysis of randomised controlled trials [2]), except for two, which were prospective cohort studies [14, 15]. All studies were published between 2019 and 2022. Four studies were from the United Kingdom [9, 17–19], two were multinational [11, 13], two from in the United States [2, 4], two from China [14, 20], one from Australia [15] and one from Italy [16]. The number of participants ranged from 32 to 2067, for a total study cohort of 7684. 10 out of 13 studies reported outcomes in HRs, whereas three reported ORs [11, 16, 21] and were therefore excluded from the meta-analysis.

Monocyte count thresholds

Monocyte counts were measured consistently across different studies using plasma or serum; however, the details of assays used were frequently unavailable. Monocyte counts were measured at varying timepoints, from within 30 days of diagnosis to up to 4 months within presentation to the ILD clinic. Varying monocyte counts were used in analyses; one study used the monocyte count of $>0.24\times10^9$ cells·L^{-1} [20], one study used $\geqslant0.6\times10^9$ cells·L^{-1} [13], one study used 0.6–$<0.8\times10^9$ cells·L^{-1} [2], one study used $\geqslant0.65\times10^9$ cells·L^{-1} [21], one study used $>0.67\times10^9$ cells·L^{-1} [14], two used $>0.9\times10^9$ cells·L^{-1} [17, 18], five used $\geqslant0.95\times10^9$ cells·L^{-1} [2, 4, 9, 13, 15] and one study used $>1.0\times10^9$ cells·L^{-1} [19]. Two studies reported analyses using monocyte counts defined as a continuous variable [16] or in 1SD increments [11].

Monocyte count and mortality

Data on overall mortality, with or without transplantation, were available for nine out of 13 studies included in the systematic review. One study reported transplant-free survival [4], five studies determined all-cause mortality (specified at 1 year [2, 13], 6 months [20] and an unspecified timeframe [17, 19]) and three studies reported survival as the outcome [14–16]. One study reported a composite outcome of relative FVC decline ⩾10% predicted or diffusing capacity of the lung for carbon monoxide (D_{LCO}) decline ⩾15% at 1 year, death or lung transplant.

Seven retrospective cohort studies and one prospective cohort study reported an association between elevated monocyte count and overall mortality in patients with ILD. Most of these studies included patients with IPF; however, elevated monocyte counts were also associated with higher risk of all-cause mortality in those with early fibrotic ILA [18] and decreased survival in those with fHP [9].

The pooled unadjusted HR for mortality for monocyte counts $\geqslant0.6\times10^9$ cells·L^{-1} was 1.71 (95% CI 1.34–2.19, p<0.001, I^2=0%) (figure 1). The pooled unadjusted HR for mortality was 2.44 (95% CI 1.53–3.87, p=0.0002, I^2=2%) for monocyte counts $>0.9\times10^9$ cells·L^{-1} (figure 2) and in adjusted models was 1.93 (95% CI 1.24–3.01, p=0.0038 I^2=69%) for monocyte counts $\geqslant0.95\times10^9$ cells·L^{-1} (figure 3). Heterogeneity was high in the retrospective cohort studies estimating mortality risk with elevated monocyte counts $>0.90\times10^9$ cells·L^{-1} in unadjusted models (I^2=61%) and $\geqslant0.95\times10^9$ cells·L^{-1} in adjusted models (I^2=73%). In studies that used monocyte counts $\geqslant0.6\times10^9$ cells·L^{-1} to estimate mortality, heterogeneity was low (I^2=0%), likely due to inclusion of three patient cohorts from only two separate studies, resulting in similar methodology and patient characteristics.

In contrast, one retrospective cohort study investigated patients admitted to hospital with anti-MDA5 antibody positive DM-ILD and found that low monocyte counts ($<0.24\times10^9$ cells·L^{-1}) predicted higher risk of all-cause mortality at 6 months (pooled HR 2.03, 95% CI 1.42–2.91, p<0.0001). This study utilised the shortest timeframe to determine all-cause mortality.

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TABLE 1 Study characteristics

Study, year	Included in meta-analysis	Country of study	ILD sample size	Type of ILD	Age, years	Male, %	Baseline FVC, % predicted	Baseline D_{LCO}, % predicted	Monocyte parameters	Timing of monocyte measurement	Relevant outcomes reported
Achaiah *et al.* [18], 2021	Yes	UK	32	Indeterminate UIP	76.7±6.2	66	92.6±26.9	64.2 (16)	>0.9×10^9 cells·L^{-1}	Within 3 months of initial CT	Visual increase in extent of disease or progression of CT to "definite" or "probable" UIP
Achaiah *et al.* [19], 2022	Yes	UK	1259 (mortality) 362 (progression)	Early fibrotic ILA	63.4±8.1	57.2	NA	NA	>1×10^9 cells·L^{-1}	Closest to CT; median time interval between CT and blood sample 13–30 days	Radiologic progression, all-cause mortality
Achaiah *et al.* [17], 2022 (NLR)	Yes	UK	128	IPF	74.8±6.9	79	85.5 (69.9–98.0)	6.19 (50.9–71.0)	>0.9×10^9 cells·L^{-1}	Within 4 months of presentation to ILD clinic	FVC decline >10% per year, all-cause mortality
Karampitsakos *et al.* [13], 2021	Yes	Multinational	300 (discovery) 189 (validation) 489 (pooled)	IPF	NA	NA	NA	NA	⩾0.95×10^9 cells·L^{-1} (pooled) ⩾0.6×10^9 cells·L^{-1} (discovery and validation)	Baseline (prior to antifibrotic treatment)	All-cause mortality, 1-year disease progression as assessed by functional decline
Kreuter *et al.* [2], 2021	Yes	USA (multicentre)	2067	IPF	NA	NA	NA	NA	0.6–0.8×10^9 cells·L^{-1} ⩾0.95×10^9 cells·L^{-1}	Baseline	All-cause mortality over 1 year
Scott *et al.* [4], 2019	Yes	USA (multicentre)	130 (Stanford) 36 (COMET)	IPF	NA	NA	NA	NA	⩾0.95×10^9 cells·L^{-1}	Stanford: within 30 days of diagnosis; COMET: baseline	Transplant-free survival (discovery), mortality (validation)
Teoh *et al.* [15], 2020	Yes	Australia (multicentre)	231	IPF	69.9±8.3	71	80.3±22	48.2±16.8	⩾0.95×10^9 cells·L^{-1}	Baseline	Survival
Zhang *et al.* [14], 2022	Yes	China (multicentre)	34	IPF	64.5±9.46	82.69	77.39±20.31	40.36±18.71	>0.67×10^9 cells·L^{-1}	After admission to hospital	Survival

Continued

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TABLE 1 Continued

Study, year	Included in meta-analysis	Country of study	ILD sample size	Type of ILD	Age, years	Male, %	Baseline FVC, % predicted	Baseline D_{LCO}, % predicted	Monocyte parameters	Timing of monocyte measurement	Relevant outcomes reported
Barratt *et al.* [9], 2021	No	UK	281	fHP	70 (65–80)	41	79 (65–94)	50 (43–64)	$\geqslant 0.95\times10^9$ cells·L^{-1}	At the point of diagnosis	Survival
Bernardinello *et al.* [16], 2022	No	Italy	77	Newly diagnosed IPF	70 (53–81)	83	80 (50–125)	57 (30–106)	Continuous	At diagnosis and within at least 1 year following antifibrotic therapy	FVC decline ⩾5% predicted over 1 year
Kim *et al.* [11], 2021	No	Multinational	1659	ILA	78±6	55	NA	NA	1SD increment	At first clinic visit	ILA progression
Lv *et al.* [20], 2022	No	China	351 (pooled)	Anti-MDA5 positive DM-ILD	53.11±11	33.6	NA	NA	$>0.24\times10^9$ cells·L^{-1}	Weekly for first 4 weeks of hospital admission	6-month all-cause mortality
Shao *et al.* [21], 2022	No	Austria	95 (derivation)	Fibrotic ILD	70.9±1.5	66.6	81±3.1	54.8±2.7	$\geqslant 0.65\times10^9$ cells·L^{-1}	Baseline	Relative FVC decline ⩾10% or D_{LCO} decline ⩾15% at 1 year, death or lung transplant

CT: computed tomography; D_{LCO}: diffusing capacity of the lung for carbon monoxide; DM: dermatomyositis; fHP: fibrotic hypersensitivity pneumonitis; FVC: forced vital capacity; ILA: interstitial lung abnormalities; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; MDA5: melanoma differentiation-associated gene 5; NA: not applicable/available; UIP: usual interstitial pneumonia.

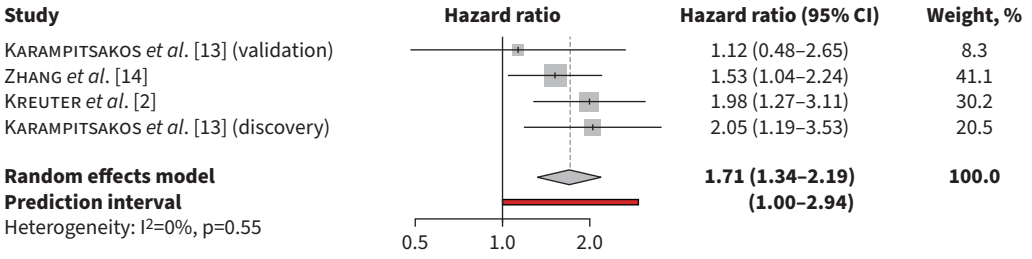

FIGURE 1 Risk of mortality associated with monocyte counts ⩾0.6×10^9 cells·L^{-1} in unadjusted models.

Monocyte count and disease progression

Seven out of 13 studies in the systematic review assessed disease progression. Definitions of disease progression varied, from radiologic progression to decline in FVC or D_{LCO}. Three of the seven studies investigated IPF and found an association between elevated monocyte count and disease progression [13, 16, 17]. Two studies investigated ILA. Achaiah *et al.* [19] reported an association between monocyte counts >1.0×10^9 cells·L^{-1} and radiological progression in patients with early fibrotic ILA (HR 1.72, 95% CI 1.10–2.69, p=0.018), while Kim *et al.* [13] reported that higher monocyte counts (analysed in increments of 1SD) were associated with ILA progression when adjusted for age, sex, smoking status, cigarette pack-years and body mass index (OR 1.3, 95% CI 1.1–1.5, p=0.001). Shao *et al.* [21] determined that in patients with radiographic evidence of fibrosis (defined as the presence of reticular lung abnormalities or honeycombing on high-resolution computed tomography), baseline monocyte counts ⩾0.65×10^9 cells·L^{-1} were associated with worse prognosis (OR 3.16, 95% CI 1.27–7.88, p=0.014). Achaiah *et al.* [18] found that monocyte counts >0.9×10^9 cells·L^{-1} were associated with radiologic progression in patients with a radiological pattern of indeterminate UIP.

Similarly, disease progression definitions differed across the four studies included in the meta-analysis, including radiographic extent of disease and physiologic parameters (⩾10% absolute decline in FVC per year or change in 6-min walk distance). Variable monocyte counts were used, including >0.9×10^9, ⩾0.95×10^9 and >1.0×10^9 cells·L^{-1}, which are pooled together here. Three of the four studies reported analysis from adjusted models, whereas one reported results from an unadjusted model, and these were pooled. The pooled HR for disease progression was 1.83 (95% CI 1.40–2.39, p<0.0001, I^2=28%) (figure 4).

Risk of bias

A comprehensive risk of bias assessment of the included studies revealed several limitations and possible biases (supplemental table 2), but, overall, the results were similar across the publications included for analysis. Visual inspection of funnel plots implied that some publication bias was present for studies included in the mortality risk and disease progression assessment (supplemental figures 2–5).

Discussion

In this first systematic review and meta-analysis of monocyte counts and outcomes in patients with ILD, elevated baseline peripheral blood monocytes were associated with higher risk of death and disease

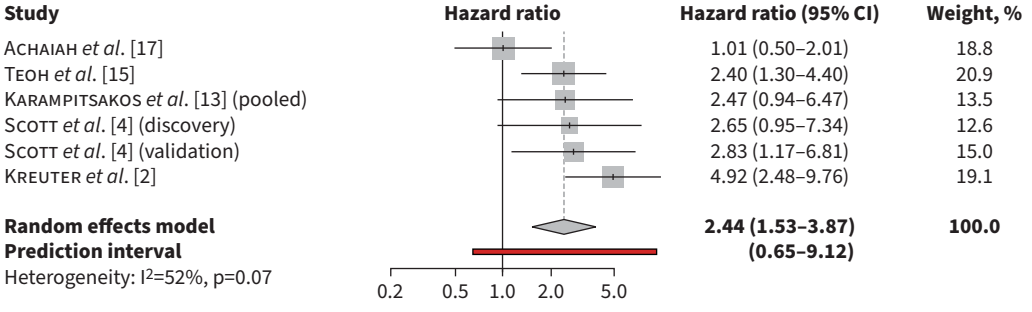

FIGURE 2 Risk of mortality associated with monocyte counts >0.9×10^9 cells·L^{-1} in unadjusted models.

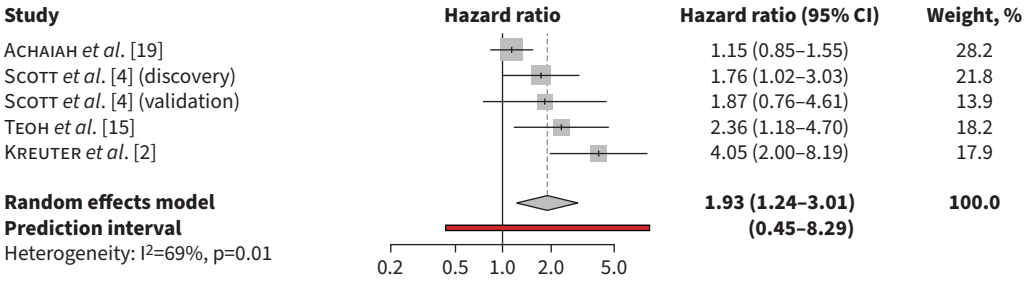

FIGURE 3 Risk of mortality associated with monocyte counts ⩾0.95×10^9 cells·L^{-1} in adjusted models.

progression. However, the higher monocyte count threshold of >0.9×10^9 cells·L^{-1} demonstrated greater consistency in its association. These data inform the role of peripheral blood monocyte counts to be used as an important and readily available prognostic biomarker in ILD.

These findings suggest a relationship between monocyte counts and ILD prognosis, supporting the possible role of monocytes in the pathogenesis of ILD. Numerous immune cells have been implicated in the development of IPF, including monocytes, neutrophils and lymphocytes [6, 22]. Although immunosuppressive treatments are associated with increased mortality in patients with IPF [23], the innate immune system appears to be involved in establishing fibrosis. Historically, fibrogenesis due to repeated lung injury has been described. Within this model, monocytes migrate to the injured lung, differentiate into macrophages and coordinate a profibrotic and pro-inflammatory response [24, 25].

Monocytes are a plastic cell population with the ability to differentiate into different subtypes, including pulmonary macrophages, depending on the context of their activation [26]. Pulmonary macrophages may be further distinguished by surface markers into alveolar macrophages, interstitial macrophages and monocyte-derived macrophages, with an ability to transition from one phenotype to another [27]. Functionally, pulmonary macrophages have been characterised as classically (M1) or alternatively (M2) activated and may demonstrate dynamic activation depending on disease context [27]. Progression of pulmonary fibrosis has been linked with changes in both the phenotype and function of pulmonary macrophages [22, 28] with alveolar epithelial cells and fibroblasts also playing contributing roles [27, 29, 30]. These alterations in pulmonary macrophages may be partially driven by changes in monocyte subtype populations [2, 22, 26].

Supporting this hypothesis, significant differences in cell and molecular markers involved in monocyte/macrophage activation and recruitment were found between patients with IPF and normal subjects [5, 31]. Immune phenotyping of peripheral blood monocytes of IPF patients showed increased expression of CD64 protein and type 1 interferon response compared to age-matched controls [31].

In murine models, monocyte-derived macrophages appear to drive the development of pulmonary fibrosis [22, 32]. Monocyte-driven changes in airway macrophages have also been associated with aging [33–35]. Pulmonary accumulation of distinct alveolar macrophages has also been associated with worse clinical outcomes [36].

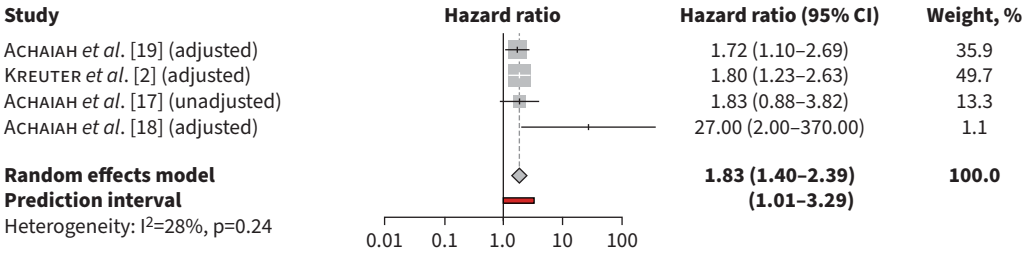

FIGURE 4 Risk of disease progression associated with monocyte counts >0.90×10^9 cells·L^{-1} in unadjusted and adjusted models.

The outcomes reported by each study in this review differed in that variable definitions of disease progression and mortality were used. Only one study reported transplant-free survival [4], whereas others reported all-cause mortality. Importantly, the included studies often had not adjusted for the same potentially confounding variables. Two out of seven studies adjusted for treatment status [2, 14], while one study included treatment-naïve patients with IPF, but the timing of monocyte count measures in relation to drug treatments were not clear. Studies were observational retrospective cohort studies and of small to modest size. Monocyte counts at baseline were measured at different timepoints across different studies, from within 30 days of diagnosis to within 4 months of presentation to an ILD clinic. Finally, out of the seven included studies, only two included cohorts with non-IPF ILDs (indeterminate UIP and early fibrotic ILAs), limiting the generalisability of these findings.

Previously, a change in monocyte count from baseline over 1 year was found to not be associated with increased mortality or disease progression [2]. Further research into the relationship between monocytes and ILD prognosis, particularly in the context of treatment and with longitudinal follow-up, may clarify whether monocyte counts could function as a predictor of therapeutic response. Additionally, it is unknown if the elevated monocyte counts are causal of poor outcomes or reflective of an underlying disease process. This warrants further investigation to understand if targeting of monocytes or their subsets could have positive therapeutic effects.

This study has limitations, largely relating to the low numbers of parent studies included for analysis and quality of the parent data. There was relatively high heterogeneity in the pooled estimates of mortality in adjusted and unadjusted models associated with elevated monocyte count. In addition, due to small study numbers, meta-regression or detailed exploration of heterogeneity was not possible. This heterogeneity was expected, however, given the variability in analytic approaches and reported outcomes of the included studies. Elevated monocyte count thresholds were variably defined across the studies, including 0.9×10^9, 0.95×10^9 and 1.0×10^9 cells·L^{-1}. The HRs of these varying thresholds were pooled due to the few numbers of studies available and residual confounding is possible.

In summary, this systematic review and meta-analysis found that baseline elevated monocyte counts are associated with worse clinical outcomes in patients with ILD and ILA. The absolute monocyte count is promising as a simple and effective biomarker of ILD prognosis. Further prospective studies are needed to better characterise this relationship and determine if it holds true across ILD subtypes and whether it is impacted by ILD-targeted treatment.

Points for clinical practice and questions for future research

- Elevated baseline peripheral blood monocyte counts are associated with increased risk of death and disease progression in patients with ILD or ILA.
- Prospective studies are needed to further characterise this relationship, accounting for concomitant treatments and ILD subtypes.
- Future work should evaluate for specific monocyte cell subsets to characterise the pathobiology of this relationship and determine whether monocytes are pathogenic or a marker of disease activity.

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Conflict of interest: All authors have nothing to disclose.

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