Supplementary data

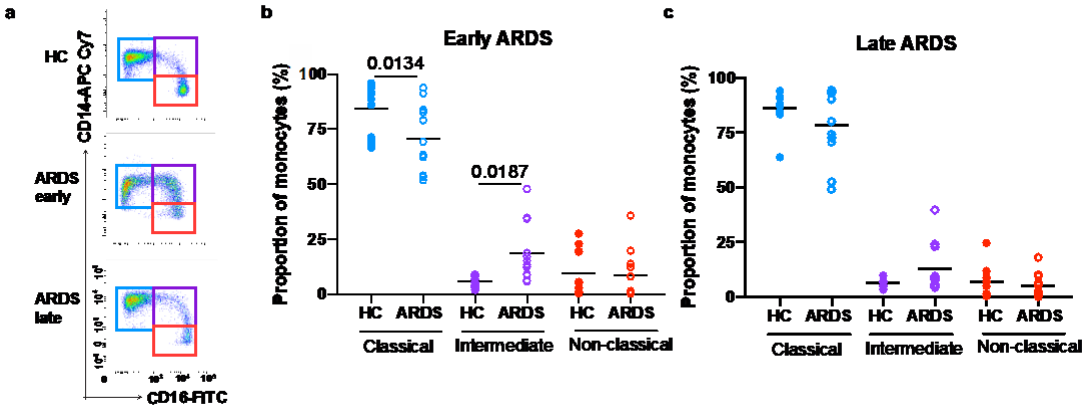

Figure S1. Monocyte sub-populations are altered early in ARDS

(**a**) Representative plots and proportions of monocyte sub-populations based on CD14 and CD16 expression early and (**b**) late (**c**). **b**, **c** one-way ANOVA with Holm-Sidak post-test.

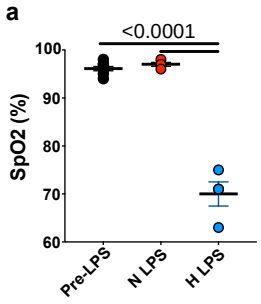

Figure S2. Oxygen saturations in mice post LPS injury (**a**) Oxygen saturations in mice were measured in mice at baseline pre-LPS nebulisation (pre-LPS) and 6 hours post-LPS (N LPS- mice housed in normoxia post-LPS, H LPS- mice housed in hypoxia post-LPS). (Pre-LPS n=6, N LPS n=3, H LPS n=3). Statistical testing performed using one-way ANOVA with Tukey's multiple comparisons test.

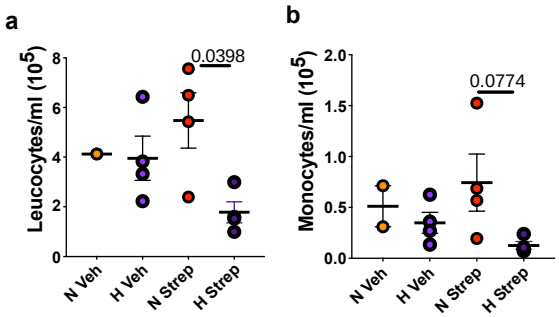

Figure S3. *Streptococcus pneumoniae* infection in hypoxia leads to leukopenia and monocytopenia. Mice were inoculated with *Streptococcus pneumoniae* (Strep) or vehicle (Veh) intratracheally (i.t.) and housed in normoxia (N) or hypoxia (H) until 24 hours post-i.t. (**a**) Blood cell counts and (**b**) monocyte counts mice housed in normoxia (N) or hypoxia (H) for 24 hours (Veh N and H n=4, Strep N and H n=6). Statistical testing performed using one-way ANOVA with Tukey's multiple comparisons test.

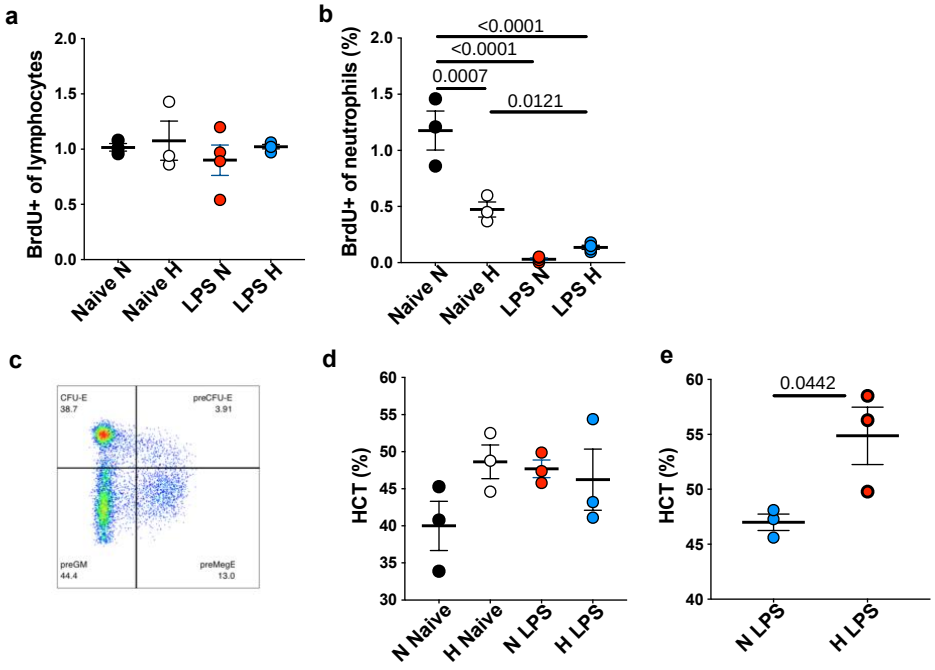

Figure S4. Impact of hypoxia on bone marrow cell egress and composition (**a**) BrdU+ blood lymphocytes (CD3 and $CD19^{+}$) and (**b**) BrdU+ blood neutrophil proportion in mice treated with LPS and housed in normoxia (N) and hypoxia (H) for 24 hours (Naïve N and H n=3, LPS N and H n=4). Data representative of 2 experiments (**c**) gating strategy for bone marrow common myeloid progenitor progeny on $CD41^{-}$ $CD16/32^{-}$ cells. (**d**) blood hematocrit at 24 hours (n=3/ group) data representative of 3 experiments or (**e**) 5 days in mice treated with LPS and housed in normoxia (N) and hypoxia (H) (n=3/group). Data representative of 2 experiments (**a**, **b**) Statistical testing performed using one-way ANOVA with Tukey's multiple comparisons test, (**e**) statistical testing performed using two-tailed unpaired t-test.

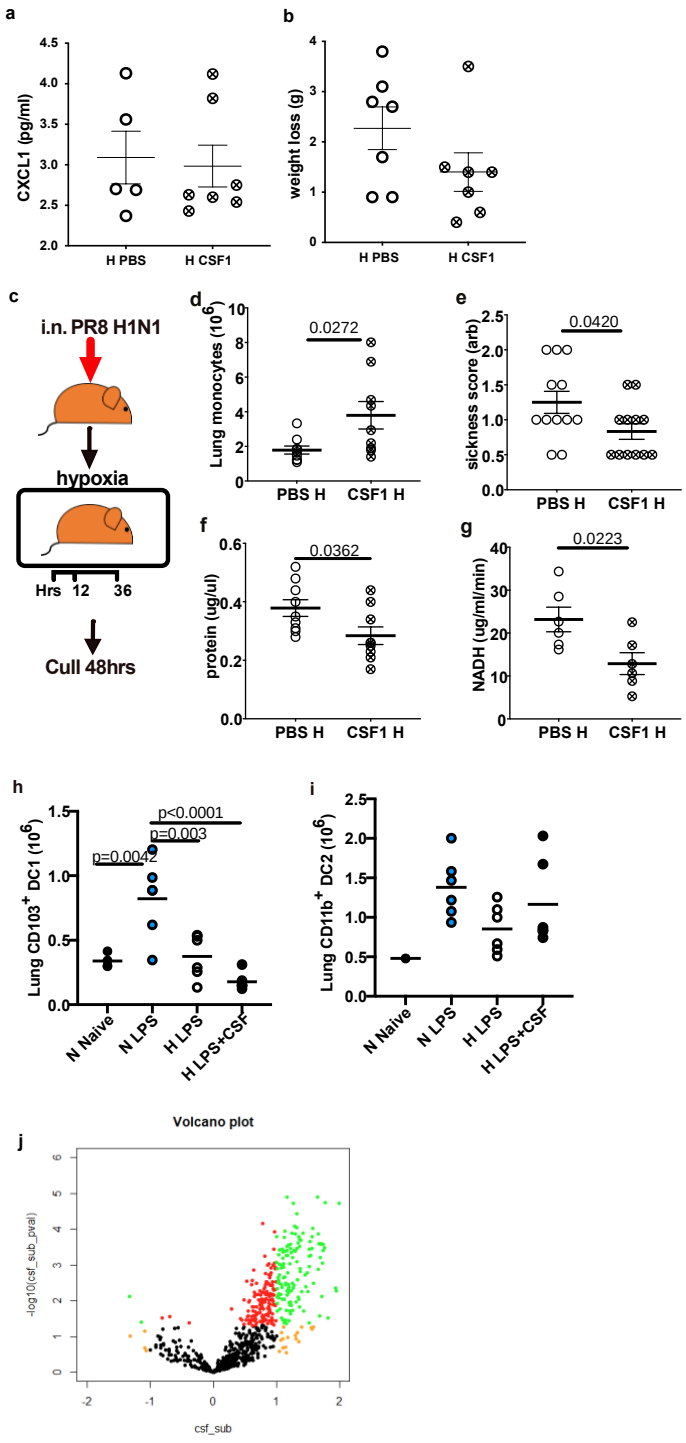

Figure S5. CSF1-Fc alters monocyte phenotype and improves injury outcomes

(**a**) BAL CXCL1 (**b**) weight loss in hypoxic LPS-induced ALI treated with PBS (H PBS) or CSF1 (H CSF1)(**c**) Schematic of virally-induced ALI plaque-forming units (p.f.u.).

(**d**) Lung monocyte numbers, (**e**) arbitrary sickness scores, (**f**) BAL protein and (**g**) LDH activity (as measured by NADH) were measured at 48 hours in mice with virally-induced ALI housed in hypoxia and receiving either PBS or CSF1. **(h**) Lung cDC1 (gated on Alive $CD45^{+}$Lin-$CD64^{-}CD11c^{+}Cd103^{+}$) and (**i**) cDC2 (gated on Alive $CD45^{+}$Lin-$CD64^{-}CD11c^{+}Cd103^{-}$ $CD11b^{+}$) chimerism relative to blood monocyte chimerism in non-LPS-treated (naïve) or LPS-treated mice housed in normoxia (N) or hypoxia (H) and receiving PBS or CSF1. (**j**) Volcano plot of measured genes in classical monocytes from mice treated with LPS and housed in hypoxia for 5 days and treated with PBS or CSF1-Fc for 4 days. Green dots correspond to genes with log2 change > 1 or < -1 and with p values <0.05. Orange dots denote genes changing > 1 or < -1 with p values >0.05. Red dots denote genes with log2 changes out-with the differential expression range but with p values <0.05. Data shown as mean ±SEM with each data point representing an individual mouse. Statistics **d** two-tailed Mann-Whitney following D'Agostino & Pearson normality test, **f**, **g** One way ANOVA with Tukeys' multiple comparisons test, **h, l**iOne way ANOVA with Kruskal-Wallis multiple comparisons test.

Table S1. Patient demographics, clinical severity and oxygenation

Group	Gender	Age	APACHE II score	Lowest recorded PaO2 prior to sampling	FiO2(%) at time of pre-sample oxygenation recording	Cause of ARDS: Pulmonary or Extrapulmonary
Early	F	58	19	9.8	70	Extrapulmonary
Early	M	78	31	8.1	100	Extrapulmonary
Early	M	73	19	9.1	21	Pulmonary
Early	F	46	15	10	100	Pulmonary
Late	M	72	21	7.9	40	Extrapulmonary
Late	F	72	17	9.1	35	Extrapulmonary
Late	M	74	9	8.9	40	Extrapulmonary
Late	F	53	30	6.9	45	Extrapulmonary
Early	M	63	19	9	25	Pulmonary
Late	M	49	16	7	45	Pulmonary
Early	F	72	29	7.3	80	Pulmonary
Late	M	57	38	8.4	60	Pulmonary
Early	F	51	24	7.8	30	Pulmonary
Early	M	67	21	9.2	50	Pulmonary
Early	F	42	21	12	70	Extrapulmonary
Early	M	54	7	6.1	70	COVID+ ARDS
Late	F	41	13	9.7	60	COVID+ ARDS
Late	M	32	21	14.1	55	Extrapulmonary
Early	M	54	27	8.4	30	Pulmonary
Early	F	56	13	9.5	45	COVID+ ARDS
Late	F	60	13	7.7	35	Extrapulmonary
Late	M	53	18	15	75	Pulmonary
Late	M	53	11	8.2	60	Pulmonary