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Clonal hematopoiesis of indeterminate potential and risk of death from COVID-19

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Clonal hematopoiesis is an age-related phenomenon in which a clonal population of blood cells emerges and is often detected by the presence of a mutation present in a peripheral blood sample. Clonal hematopoiesis of indeterminate potential (CHIP) is a subtype of clonal hematopoiesis found in individuals without a hematologic malignancy in which a somatic pathogenic mutation in a gene mutated in myeloid neoplasia is present in at least 2% of the sequenced blood DNA (termed variant allele fraction [VAF]).1,2 CHIP is associated with increased mortality and risk of adverse outcomes including cardiovascular and pulmonary disease (eg, chronic obstructive pulmonary disease).3-5 These associations, which are largely driven by CHIP clones with a VAF of greater than 0.1, are thought to arise from augmentation of inflammasome-mediated interleukin-1β (IL-1β) and IL-6 production by mutant macrophages.4,7

Complications from COVID-19 are thought to result from an enhanced inflammatory state, potentially mediated by macrophage activation and elevated levels of IL-6, though clinical trials assessing the clinical benefit of IL-6 blockade in patients with COVID-19 have yielded conflicting results.3,8-16 Clinical risk factors for poor outcomes from COVID-19 include older age, cardiovascular disease, and pulmonary disease. Given the shared risk factors between CHIP and COVID-19 severity, we examined whether there was an association between CHIP and risk of death in patients hospitalized with COVID-19.

The Massachusetts General Brigham cohort included patients hospitalized between March 10, 2020, and April 4, 2021, at Brigham and Women’s Hospital (BWH) and Massachusetts General Hospital (MGH) (Figure 1A). All studies were performed with institutional review board approval. Clinical and laboratory data were obtained using the Massachusetts General Brigham Electronic Data Warehouse.17 The tocilizumab cohort included patients from a randomized trial assessing the efficacy of tocilizumab in patients with COVID-19 (supplemental Figure 1, available on the Blood website).10 Genomic sequencing to identify the presence of CHIP was performed on all samples using either whole genome or targeted as previously described (supplemental Tables 1 and 2).18-20 The primary end point was the association between CHIP with a VAF of 0.1 or greater and in-hospital mortality within 28 days of admission. We used multivariable logistic regression to adjust for age at blood draw, sex, cardiovascular disease, pulmonary disease, diabetes, cancer, and admitting hospital.6,5 Exploratory end points were evaluated using a Wilcoxon rank-sum test when continuous and a Fisher’s exact test when categorical. A P value of less than .05 was considered statistically significant. Additional information for all methods can be found in the supplemental Methods.

Our final cohort included 1338 patients (BWH, n = 530; MGH, n = 758) who did not have a hematologic malignancy, were admitted for at least 24 hours, and had a peripheral blood sample available. The majority of patients had a blood draw on the day of admission (median time between blood draw and admission, <1 hour; interquartile range, <24 hours). The cohort characteristics are shown in supplemental Table 3.

CHIP was identified in the BWH patients using a targeted sequencing platform and in the MGH patients using whole genome sequencing (see supplemental Methods). Given the stronger associations reported for larger CHIP clones with adverse outcomes, our primary analyses focused on CHIP clones with a VAF of 0.1 or greater.4,5 We identified 73 individuals (5.5%) with CHIP at a VAF of 0.1 or greater, with most mutations occurring in DNMT3A, TET2, and ASXL1 (Figure 1B, supplemental Table 4).

Individuals with CHIP at a VAF of 0.1 or greater were significantly older (median age, 74.0 years vs 61.3 years; P < .001) and more likely to have a history of cardiovascular disease (46.6% vs 33.7%; P = .03) (supplemental Table 5; supplemental...
In univariable analysis, older age (odds ratio [OR], 4.2 for age ≥ 65 years old; 95% confidence interval [CI], 2.9-6.1; \(P < .001\)), a history of cardiovascular disease (OR, 1.7; 95% CI, 1.2-2.3; \(P = .002\)), renal disease (OR, 1.8; 95% CI, 1.1-3.0; \(P = .014\)), and cancer (OR, 1.7; 95% CI, 1.0-2.7; \(P = .029\)) were significantly associated with an increased risk of 28-day mortality, whereas CHIP with a VAF of 0.1 or greater was not (OR, 0.76; 95% CI, 0.3-1.6; \(P = .50\)) (supplemental Table 6).
**Figure 2.** *IL6R* D358 SNP A/A is associated with increased 28-day in-hospital mortality in the primary cohort. (A) Forest plot of multivariable analysis within Massachusetts General Brigham (MGB) cohort (adj *P* value, adjusted *P* value). (B) Cumulative 28-day mortality among patients with *IL6R* D/D, D/A, and A/A in the MGB cohort. (C) Distribution of genes mutated in patients found to have CHIP with a VAF of 0.02 or greater in the tocilizumab cohort. (D) Comparison of mutant VAF between day 1 and late timepoint in serial samples from the tocilizumab cohort (see supplemental Figure 5).
In multivariable analysis only age (OR, 4.1 for age ≥65 years old; 95% CI, 2.8-6.1; P < .001) was significantly associated with an increased risk of 28-day mortality (Figures 1C-D), whereas CHIP with a VAF of 0.1 or greater was not (OR, 0.53; 95% CI, 0.21-1.1; P = .121). Exploratory analysis of patients aged more than 65 years, those with a DNMT3A-mutant CHIP (VAF ≥ 0.1), or those with CHIP at a VAF of 0.05 or greater also showed no association between CHIP and 28-day mortality (supplemental Figures 2C, 3A-C, and 4A-B; supplemental Table 7).

We genotyped all patients for the IL-6 receptor (IL6R) D358A single nucleotide polymorphism (SNP) that is associated with decreased IL-6 signaling and a decreased risk of adverse cardiovascular outcomes.4,22 In multivariable analysis, the risk of decreased IL-6 signaling and a decreased risk of adverse cardiac outcomes in prior studies.4,5 Finally, our analyses were not mechanistic work to understand this association is needed.25 A recent study using the UK Biobank found no association between impaired IL-6 signaling and death or need for intubation in patients with COVID-19, but did find an association with increased risk of hospitalization and infection, a question our study was not designed to address.25

Our study has several limitations. The study was performed retrospectively, but did include patients admitted over a year to 2 separate hospitals. Additionally, a 28-day in-hospital mortality primary end point may have missed patients who died after discharge from the hospital. We also did not assess smaller CHIP clones, given their weak associations with adverse outcomes in prior studies.4,5 Finally, our analyses were not structured to interrogate causality or define specific mechanisms that may link CHIP or the IL6R D358A SNP to mortality, but was rather performed to identify the presence of an association that could have implications for risk stratification and defining future clinical and basic studies.

Taken together, our data do not support an association between the presence of clonal hematopoiesis and the risk of 28-day mortality in patients with COVID-19, but do support the potential role of IL-6 signaling in mediating patient outcomes.

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Authorship
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