Abstract: P1342

Title: THE IMPACT OF CLONAL HEMATOPOIESIS ON THE RISK OF SEVERE COVID-19 INFECTION

Abstract Type: Poster Presentation

Session Title: Hematopoiesis, stem cells and microenvironment

Background:

Clonal hematopoiesis (CH) associated with aging has been highlighted because it correlates not only with leukemia development, but also with non-malignant conditions. Of particular interest of recent years among these CH-associated diseases is COVID-19. To date, significant associations have been reported between COVID-19 and CH-related gene mutations or copy-number alterations (CNAs). However, the joint effect of both lesions has not been evaluated. Moreover, the mechanism of increased risk of severe COVID-19 under the presence of CH is still unknown.

Aims:

We aimed at revealing the joint effect of gene mutations and CNAs on the risk of severe COVID-19 and elucidating the mechanisms of increased risk of severe COVID-19 conferred by CH.

Methods:

We performed an integrated analysis of CH-related mutations and CNAs in 4,542 patients with COVID-19 infection, among whom 54% had severe symptoms. Gene mutations and CNAs were detected using targeted-capture sequencing of 42 driver genes and SNP-array-based copy-number analysis, respectively. We also performed plasma proteome analysis for 2,927 proteins in 1,200 patients.

Results:

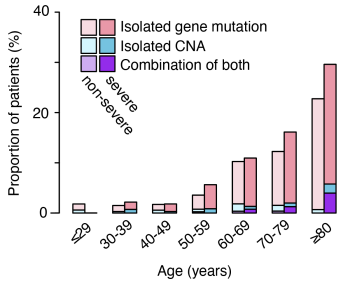
We identified gene mutations and CNAs in 16.5% and 6.2% of COVID-19 patients, respectively. Cooccurrences of both types of lesions were detected in 2.4%. As reported in CH in normal individuals, most frequent alterations included mutations in DNMT3A (7.6%), TET2 (4.1%), ASXL1 (1.4%), PPM1D (1.7%), and CNAs such as 14qUPD, and del(20q).

To evaluate the risk of severe COVID-19 conferred by CH, we compared the age-stratified frequencies of CH between severe and non-severe COVID-19 patients. Focusing on CH in ≧10% clonal fractions, CH was significantly enriched in severe COVID-19 in elderly patients, which was explained by the enrichment of combinations of gene mutations and CNAs, and isolated gene mutations, but not that of isolated CNAs (Figure). Then, we performed multivariable logistic regression with adjustment for age and sex, revealing the presence of CH was associated with severe COVID-19 with an odds ratio (OR) of 1.34 [95%CI=1.03–1.84] in patients aged ≥65 years. Particularly, combinations of gene mutations and CNAs conferred a remarkable increase in the risk of severe COVID-19 [OR=12.1, 95%CI=1.61–90.6], suggesting their combinations may further promote the development of severe symptoms.

To elucidate the mechanism behind the increased risk in CH, we next evaluated the changes in proteomic profiles associated with severe COVID-19 and CH by gene-set enrichment analysis for 50 hallmark gene sets. As previously reported, proteins upregulated in severe COVID-19 were enriched for those implicated in the signaling by inflammatory cytokines including IL-6, interferon-γ, and TNF-α. As for the changes associated with CH, we identified upregulation of several pathways, among which only IL-6 signaling was relevant to inflammatory signaling. As commonly seen in severe COVID-19 and CH, enhanced IL-6 signaling can be a potential mechanism of increased risk of severe COVID-19 in patients with CH. In addition, upregulation of IL-6 signaling was more prominent when gene mutations and CNAs were combined, corresponding to the particularly high risk of severe COVID-19 in those with both alterations.

Summary/Conclusion:

In conclusion, our integrated analysis of gene mutations and CNAs in COVID-19 patients revealed increased risk of severe COVID-19 in CH, which was remarkable when gene mutations and CNAs were combined. The plasma proteomic analysis suggested enhanced IL-6 signaling is a potential mechanism of the increased risk of severe COVID-19 mediated by CH, warranting further investigations.



Keywords: Gene mutation, Clonal hematopoiesis of indeterminate potential, Chromosomal abnormality, COVID-19