# Minor allele of Intercellular adhesion molecule-1 (ICAM-1) polymorphism (rs5498 1462A>G) is associated with SARS-CoV-2 infection and related mortality.

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Dear Editor,

We were intrigued by the article by Tong et al.[1] article because it established the critical role of intercellular adhesion molecule-1 (ICAM-1) in the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The soluble ICAM-1 levels were elevated in severe clinical phenotypes in comparison to mild infection. Further, after treatment of SARS-CoV-2 infected patients, the sICAM-1 levels significantly declined [1]. In addition, another independent study in the American population showed higher levels of sICAM-1 in severe SARS-CoV-2 infected patients than in healthy controls[2]. Interestingly, another three-month follow-up study in a small cohort of Chinese SARS-CoV-2 recovered patients demonstrated that patients with severe disease had higher levels of sICAM-1 than patients with mild clinical conditions[3]. Levels of sICAM-1 in subjects have been associated with a common single nucleotide polymorphism at +1462 nucleotide position (A>G) in ICAM-1 gene lead to a change in 468$^{th}$ amino acids from lysine (K) to glutamic acid (E). Heterozygous mutant (469KE) and homozygous mutant (469EE) are linked with elevated sICAM-1 in comparison to the wild type (469KK)[4, 5]. Based on these observations, we hypothesized that ICAM-1 genetic variant (K469E) would be associated with predisposition to SARS-CoV-2 infections, clinical severity, and related mortality in the worldwide population.

To obtain the prevalence of the minor allele for ICAM-1 rs5498 polymorphism, databases such as dbSNP and 1000 genomes were extensively screened and different data such as number of healthy controls, genotype data or allele data were collected. A total of 31 reports from 23 different countries were obtained from dbSNP and 1000 genomes database. In addition, the distribution of different genotypes was investigated for Hardy Weinberg equilibrium (HWE) and observations that deviated from HWE (data of Bangladesh and Pakistan) were omitted from the analysis (Supplementary Table-1). Data of 44017 healthy

controls were considered in the present study from 21 different countries. The minor allele (G) prevalence ranged from 8.1% to 72.4% in the included reports. The SARS-CoV-2 infection and related mortality data are available on the Worldometer website (https://www.worldometers.info/coronavirus/) and updated on a daily basis. Various data such as country name, SARS-CoV-2 infection per million, death per million of 21 countries (Gambia, Kenya, Nigeria, Sierra Leone, China, Japan, South Korea, Vietnam, Denmark, Estonia, Finland, Italy, Netherlands, Spain, United Kingdom, Cuba, Dominica, Mexico, USA, Colombia, Peru) were noted for analysis (assessed on 09$^{th}$ May 2021) (Supplementary Table-2).

The Spearman rank correlation analysis of minor allele (G) with rate of SARS-CoV-2 infection per million (r=0.535, *p*=0.012) and related mortality rate per million of population (r=0.633, *p*=0.002) showed a strong positive correlation (Figure-1), suggesting that ICAM-1 rs5498 variants may play a role in susceptibility to SARS-CoV-2 infections and increased chances of SARS-CoV-2 related death.

The mechanism by which the minor allele (G) of ICAM-1 rs5498 polymorphism is linked to SARS-CoV-2 susceptibility is unknown. The minor allele (G) has been linked to higher sICAM-1 levels in previous reports [4, 5]: subjects with heterozygous (KE) or homozygous mutant (EE) genotype have higher sICAM-1 and raise the infectivity of human immunodeficiency virus-1 [6] and facilitate the replication of influenza[7] and rhinovirus[8] in the early stage of infection. In comparison to the wild genotype, the subject mutant for the rs5498 polymorphism could have increased the risks of SARS-CoV-2 infection and increased the viral load. Since respiratory, renal, and liver dysfunctions are the primary cause of mortality in SARS-CoV-2 infected patients[9], and elevated ICAM-1 has been linked with multiple organ failure[10], it is conceivable that the minor allele (G) associated with higher

ICAM-1 levels predisposed mutant subjects to SARS-CoV-2 infection-related death in the worldwide population.

There are some limitations in our study that should be highlighted. First, the genotype or allele distribution of various populations was derived from online databases (1000 genomes and dbSNP), and individual genetic association case-controls studies were excluded from the report to maintain homogeneity. Second, the present work is an observational correlation analysis to determine the potential role of ICAM-1 rs5498 polymorphism with SARS CoV-2 infection and mortality; however, for the genetic predisposition investigation, a case-control study is more fitting. Third, HWE was not checked in some of the included studies due to a lack of genotype data. Fourth, other potential influencing factors for SARS-CoV-2-related mortality, such as age, ethnicity, and health-care settings, were not included in this study.

On the basis of the current study's findings and previous reports, it can be assumed that the minor allele 'G' of the ICAM-1 rs5498 polymorphism is associated with susceptibility to SARS-CoV-2 infection and subsequent mortality. However, validation of our results is required in diverse ethnic groups.

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Figure-1 Spearman rank correlation of minor allele G (rs5498) with SARS CoV-2 infection and mortality rate. SARS-CoV-2 infection and mortality rate per million data were obtained from worldometer website (assessed on 09$^{th}$ May 2021). The genotype and allele frequency of rs5848 polymorphism in healthy subjects of different countries were obtained from 1000 genome projects and the SNP database (dbSNP). The minor allele (G) was positively correlated with SARS-CoV-2 infection/million (A: r = 0.535, $p$ = 0.012, n = 21), the SARS-CoV-2 related death/millions of populations (B: r = 0.633, p = 0.002, n = 21). Significance was described as a $p$-value less than 0.05.