# A cluster of differentiation 14 (CD14) polymorphism (C-159T rs2569190) is associated with SARS-CoV-2 infection and mortality in the European population.

Abhijit Pati, Sunali Padhi, Debarchan Panda, Subham Suvankar and Aditya K Panda*

Department of Bioscience and Bioinformatics, Khallikote University, Konisi, Berhampur, Odisha, India 761008

***Corresponding Author**

Dr. Aditya K. Panda
Department of Bioscience and Bioinformatics
Khallikote University
Konisi
Berhampur, Odisha, India 761008
Mail id: **adityarmrc@gmail.com**, **akpanda@khallikoteuniversity.ac.in**
ORCID id: **0000-0002-1192-1978**

Dear Editor,

We read with great interest the recent article by Bowman et al. [1] that demonstrated the importance of soluble cluster differentiation 14 (sCD14) in the pathogenesis of severe coronavirus disease-19 (COVID-19). Subjects with SARS-CoV-2 infections displayed significantly higher levels of sCD14 compared to healthy controls. In addition, COVID-19 patients who died had higher levels of sCD14 than mild, moderate, and critical recovered patients. Monocyte and macrophage activation leads to enhancement of the TNF cascade and is possibly linked with the disease's prognosis. Recently, we have documented the functional relevance of a common single nucleotide polymorphism (SNP) in the promoter region of the CD14 gene (C-159T, rs2569190)[2]. The 'T' allele and 'TT' genotype were associated with higher sCD14 levels, and variation in the -159 position altered the transcription factors' binding [2]. These results inspired us to examine the relationship of CD14 (C-159T) polymorphism with susceptibility/resistance to SARS-CoV-2 infection and mortality in different populations.

Worldwide data on COVID-19 infections and death rates are available on the worldometer website (https://www.worldometers.info/coronavirus/). Various data such as the country's name, rate of SARS-CoV-2 infection per million, the death rate per million of the population were extracted (assessed on 26$^{th}$ January 2021). Published articles were searched through the PubMed database for CD14 (C-159T rs rs2569190) polymorphisms, and the genotype and allele data in healthy controls were extracted. Publications in which the distribution of genotypes was not following Hardy-Weinberg equilibrium (HWE) were excluded from the present study.

The data search indicated an incidence of SARS-CoV-2 infection in 221 countries comprising 100 million infected cases and more than 2 million deaths worldwide. In Europe, 48 countries have been affected by SARS-CoV-2 infections and reported 29.3 million cases and 0.67 million deaths. Out of 48 countries, the prevalence of CD14 C-159T polymorphism data was available for 21 states. Details of publications considered in the present analysis are shown in Supplementary Table 1. The frequency of the minor allele mutant allele (T) ranges from 36.47% - 52.55%.

The CD14 (C-159T) genotype distributions not following the HWE in healthy controls were excluded in the present investigation. Based on the HWE exclusion criteria, data from nine studies were omitted from the current investigation (Finland: 03, Germany: 02, Hungary: 01, Italy: 01, Serbia: 01, Spain: 01), and a total of 83 reports from 21 European countries (Supplementary Table 1) were considered for the current investigation. The Spearman rank correlation analysis revealed a positive correlation between SARS-CoV-2 infection rate per million of population and CD14 (C-159T) minor allele (T) (**r= 0.57, *p*=0.005**) (Figure-1A). Besides, the T allele of CD14 (C-159T) polymorphism was also positively linked with the SARS-CoV-2 mortality rate per million (**r= 0.61, *p*=0.003** (Figure-1B). These results collectively suggest a possible role of CD14 promoter variant with the predisposition and disease outcome of SARS-CoV-2 infections.

In line with the current observations, earlier reports also highlighted the association of homozygous mutant (TT) of CD14 (C-159T) polymorphism with susceptibility to viral and microbial infections and clinical severity such as tuberculosis [3], respiratory syncytial virus [4], and chronic hepatitis C [5]. In contrast, the CC genotype was associated with a predisposition to severe SARS in the Hong Kong population [6]. The exact mechanism of how the minor allele (T) is susceptible to SARS-CoV-2 infection is unknown. Further, we noticed a significant positive correlation between death due to SARS CoV-2 infection and the

minor allele T. As the allele T has been associated with elevated sCD14 levels[2], SARS CoV-2 infected subjects harboring the minor allele (T) possibly produce elevated sCD14, exacerbated inflammatory molecules and ultimately may lead to the poor prognosis of the patients.

The present study has several limitations. First, the analysis was performed in European countries. Other continents were not included in the current investigation due to the smaller number of published reports available in the prevalence of CD14 (C-159T) genotypes among the healthy controls (Asia: 10, Africa: 2, Australia: 2, North America: 4 and South America: 1). Second, we performed an observational correlation study to investigate the possible association of SARS CoV-2 infection and mortality; however, the case-control method is most appropriate for genetic predisposition studies. Third, other confounding factors for SARS-CoV-2 related deaths such as age, gender, health facilities, were not evaluated in the present investigation.

Based on the the present study and results of the earlier reports, it can be presumed that the T allele of CD14 -159 polymorphism is predisposed to SARS-CoV-2 infection and related mortality. However, case-control studies in different ethnic groups, including larger sample sizes, are required to validate our findings.

## References

1. Bowman ER, Cameron CMA, Avery A, et al. Levels of Soluble CD14 and Tumor Necrosis Factor Receptors 1 and 2 may be predictive of death in Severe Coronavirus Disease 2019 (COVID-19). J Infect Dis **2020**.

2. Panda AK, Tripathy R, Das BK. CD14 (C-159T) polymorphism is associated with increased susceptibility to SLE, and plasma levels of soluble CD14 is a novel biomarker of disease activity: A hospital-based case-control study. Lupus **2020**:961203320972799.

3. Zhao J, Lin G, Zhang WH, Ge M, Zhang Y. Contribution of CD14-159C/T polymorphism to tuberculosis susceptibility: a meta-analysis. Int J Tuberc Lung Dis **2013**; 17:1472-8.

4. Goutaki M, Haidopoulou K, Pappa S, et al. The role of TLR4 and CD14 polymorphisms in the pathogenesis of respiratory syncytial virus bronchiolitis in greek infants. Int J Immunopathol Pharmacol **2014**; 27:563-72.

5. Meiler C, Muhlbauer M, Johann M, et al. Different effects of a CD14 gene polymorphism on disease outcome in patients with alcoholic liver disease and chronic hepatitis C infection. World J Gastroenterol **2005**; 11:6031-7.

6. Yuan FF, Boehm I, Chan PK, et al. High prevalence of the CD14-159CC genotype in patients infected with severe acute respiratory syndrome-associated coronavirus. Clin Vaccine Immunol **2007**; 14:1644-5.

**Funding statement:** No specific funding was received to report.

**Conflict of Interest:** Authors declare no conflict of interest.

Figure 1. Correlation of minor allele T with SARS CoV-2 infection and mortality rate in European populations. SARS-CoV-2 infection and mortality rate per million data were obtained from worldometer site (assessed on 26.01.2021). Frequency of the T allele in healthy subjects of European countries was obtained from earlier published studies. Spearman rank coefficient analysis was performed to investigate the correlation of allele 'T' with SARS-CoV-2 infection/million (A: r = 0.57, $p$ = 0.005, n = 21), the mortality rate per million (B: r = 0.61, $p$ = 0.003, n = 21). A p-value of less than 0.05 was taken as significant

**Figure 1**