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Integrative Profiling of *CEACAM1* in Different Malignancies with Implications on the SARS-CoV-2 Infection Genes *ACE2* and *TMPRSS2*

CEACAM1'in Farklı Maliğnitilerde Bütünleştirici Profillendirilmesi ile SARS-CoV-2 Enfeksiyon Genleri *ACE2* ve *TMPRSS2* için Olan Çıkarımlar

Ahmet Acar

Department of Biological Sciences, Middle East Technical University, Çankaya, Ankara, Turkey.

ABSTRACT

Increasing number of evidence demonstrated increased SARS-CoV-2 infection risk in cancer. Despite various studies shed light on SARS-CoV-2 mediated pathways upregulated in cancer, there is still ongoing efforts to reveal underlying mechanisms of elevated risk for COVID-19 disease in cancer. Given critical role of *CEACAM1* in immune exhaustion and immune deregulation observed both in cancer and COVID-19, systematic characterization of *CEACAM1* in different malignancies was performed with an ultimate aim to identify the involvement of *CEACAM1* in enhanced COVID-19 susceptibility in cancer patients. Here we show that *CEACAM1* expression was upregulated in a number of TCGA samples. In addition, *CEACAM1* expression was positively correlated with SARS-CoV-2 infection genes in TCGA samples. Single-cell RNA sequencing analysis results of COVID-19 positive patients indicated upregulation of *CEACAM1* expression. Furthermore, *CEACAM1* expression was associated with *HAVCR2*, an immune checkpoint marker, and there was a correlation between *CEACAM1* and *HAVCR2* levels in different TCGA samples. Collectively, *CEACAM1* might provide increased susceptibility of COVID-19 disease in cancer patients which might be explained with its interaction with *HAVCR2*.

Key Words

SARS-CoV-2, COVID-19, *CEACAM1*, Cancer.

ÖZ

Artan sayıda kanıt kanser hastalarında SARS-CoV-2 enfeksiyonu riskini göstermiştir. Kanser hastalarında yukarı regüle edilen SARS-CoV-2 enfeksiyon yollarına ışık tutan çeşitli araştırmalara rağmen, kanser hastalarında SARS-ÇoV-2 enfeksiyonuna duyarlılığın artmasının nedenleri halen araştırılmaktadır. *CEACAM1*'in kanser ve COVID-19 hastalıklarında gözlemlenen immun tükenme ve immun deregülasyondaki kritik rolü göz önüne alındığında, *CEACAM1*'in kanser hastalarında COVID-19 duyarlılığına etkisini belirlemek için *CEACAM1*'in farklı kanserlerde karakterizasyonu gerçekleştirildi. Bu çalışmada *CEACAM1* ekspresyonunun TCGA örneklerinde yukarı regüle edildiği gösterilmektedir. Ek olarak, *CEACAM1* ekspresyonu TCGA numunelerinde SARS-CoV-2 genleri olan *ACE2* ve *TMPRSS2* ile pozitif korelasyonu gösterdi. Ayrıca, *CEACAM1* bir immun kontrol noktası belirteci olan HVCR2 ile ilişkilendirildi ve farklı TCGA numunelerinde *CEACAM1* ile *HAVCR2* seviyeleri arasında korelasyon bulundu. Sonuç olarak, bu bulgular, *CEACAM1*'in *HAVCR2* ile etkileşimi ile açıklanabilecek kanser hastalarının COVID-19'a karşı artan duyarlılığı sağlamada potansiyel bir rol oynayabileceğini göstermektedir.

Anahtar Kelimeler

SARS-CoV-2, COVID-19, *CEACAM1*, Kanser.

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Correspondence to: : A. Acar, Department of Biological Sciences, Middle East Technical University, Çankaya, Ankara, Turkey.

E-Mail: acara@metu.edu.tr

INTRODUCTION

COVID-19 disease has affected billions of people just under three years with widespread socioeconomical impact [1]. Characterization studies indicated that viral entry and viral propagation steps in COVID-19 is regulated by the activation of viral spike (S1) protein [2, 3]. This is then followed by SARS-CoV-2 S1 protein interacting with angiotensin converting enzyme 2 (*ACE2*) receptor for the viral entry [4]. Various proteases including *TMPRSS2* and furin were reported to facilitate these processes [5]. Upon viral entry, viral propagation steps modulated by the replicase proteins triggers the replication of the viral genome and translation into viral proteins responsible for the assembly of viral particles [6].

Cancer is a complex disease and increased susceptibly of COVID-19 disease for cancer patients were documented by other studies [7–10]. Due to impaired immunity in cancer patients and immune dysfunction related to the COVID-19 and other infectious diseases, cancer patients were considered in a high-risk group for developing COVID-19 disease [7, 8, 11]. Given the inflammatory nature of cancer, other infectious diseases and the cytokine storm seen in COVID-19 positive patients, studies reported elevated levels of cytokines and TNF-α in severe COVID-19 cases [12–15], suggesting cancer patients can be more prone to develop COVID-19 disease. Also, various viral entry, processing and endosomal route protein were detected to be elevated in pan-cancer samples in comparison to their healthy control [16–18]. Furthermore, pan-cancer studies revealed that SARS-CoV-2 associated genes, namely *ACE2*, *TMPRSS2*, *TMPRSS4*, were found to be upregulated in a number of TGCA samples [4, 5, 19, 20], indicating an interplay between cancer and SARS-CoV-2 infection.

Studies focusing on identifying immune landscape in COVID-19 cases linked with potential susceptibility demonstrated that the expression of immune checkpoint receptors (or immune inhibitors receptors) are upregulated in myeloid and lymphoid immune cells during the COVID-19 and other infectious diseases which was linked with pathophysiology of the disease [21–23]. One of the critical members of the immune checkpoint receptors is carcinoembryonic antigen cell adhesion molecule 1 (*CEACAM1*) which was demonstrated in chronic viral infection together with cancer through inducing T-cell exhaustion [24]. Moreover, using single-cell RNA sequencing (scRNAseq) approach, elevated *CEACAM1* expression was identified both in blood and bronchoalveolar samples of COVID-19 patients and correlated with enhanced viral load [25]. Increased *CEACAM1* expression was also demonstrated to play a role in immune evasion, cancer progression and immune checkpoint modulation [26–28]. Based on the involvement of *CEACAM1* in T cell exhaustion, *CEACAM1* has taken a considerable attention as a plausible target in immunotherapy in cancer [29].

Given the potential link provided by previous studies on *CEACAM1* expression in immune dysfunction and cancer, we sought to characterize the potential involvement of *CEACAM1* expression with SARS-CoV-2 infection genes, *ACE2* and *TMPRSS2*, in different malignancies. Our findings indicate that *CEACAM1* is overexpressed in multiple TCGA samples and correlated with *ACE2* and *TMPRSS2*. Moreover, scRNAseq analysis results of COVID-19 positive patients revelated elevated expression of *CEACAM1* in squamous epithelial cells, suggesting the involvement of *CEACAM1* in COVID-19 pathogenesis. Importantly, increased *CAECAM1* expression resulted in poor survival in LGG and KIRP patients. The analysis on gene network demonstrated the association of expression levels of *CEACAM1* primarily with *HAVCR2*, known immune checkpoint marker. Lastly, *HAVCR2* expression was found to be correlated with SARS-CoV-2 infection genes, *ACE2* and *TMPRSS2*, and exhibited poor survival in LGG and UVM patients. Taken together, these findings suggest that *CEACAM1* might involve in modulating increased COVID-19 seen cancer patients presumably via its association with *HAVCR2*.

MATERIALS and METHODS

The TIMER2.0 database analysis

In this study, the TIMER2.0 database was utilized. This database offered integrative analysis platform for cancer exploration in different human malignancies [30]. To assess correlation coefficient between the mRNA expression levels of *CEACAM1*, *HAVCR2*, *ACE2*, and *TMPRSS2* genes cancer exploration module was used. In this analysis, Spearman correlation indicated the degree of correlation and $p<0.05$ was considered as significant (colored as red when there was a positive correlation and colored as blue when there was a negative correlation).

HCCDB database

HCCDB platform is developed as a web-based tool mainly for the analysis of the expression atlas of hepatocellular carcinoma, however it also includes RNA-seq data for different human normal tissue samples [31]. Differential gene expression of *CEACAM1* in normal samples from various human tissues was analyzed in log2 intensity.

The UCSC cell browser for single-cell RNA expression analysis

The cell browser provided by UCSC is an interactive web-based tool and enables single-cell RNA expression data visualization and metanalysis results associated with it [32]. *CEACAM1* expression mRNA expression at the single cell level obtained from airway cells of the lung tissue in COVID-19 positive patients [33] were visualized using this platform.

Survival analysis

The TIMER2.0 database is an interactive web-based platform for survival analyses based on mRNA expression levels [30]. Prognostic impact based on survival analyses of the expression levels of *CEACAM1* and *HAVCR2* were identified using this platform.

GENEMANIA gene interaction analysis

GENEMANIA (https://genemania.org) is an interactive tool providing an in-depth information about a gene network analysis based on co-expression, physical interaction, genetic interaction, colocalization, pathway analysis and predicted features [34]. *CEACAM1* interacting partners were identified using this interactive web-based platform.

Statistical analyses

The results obtained from various TCGA expression databases provided a P value whereby *P<0.5, ** P<0.01, ***P<0.001 as significant. Spearman correlation analysis indicating Rho value: 0.00-0.19 (very weak), 0.20-0.39 (weak), 0.40-0.59 (moderate), 0.60-0.79 (strong), 0.80-1.0 (very strong) was followed. p<0.05 was considered as significant.

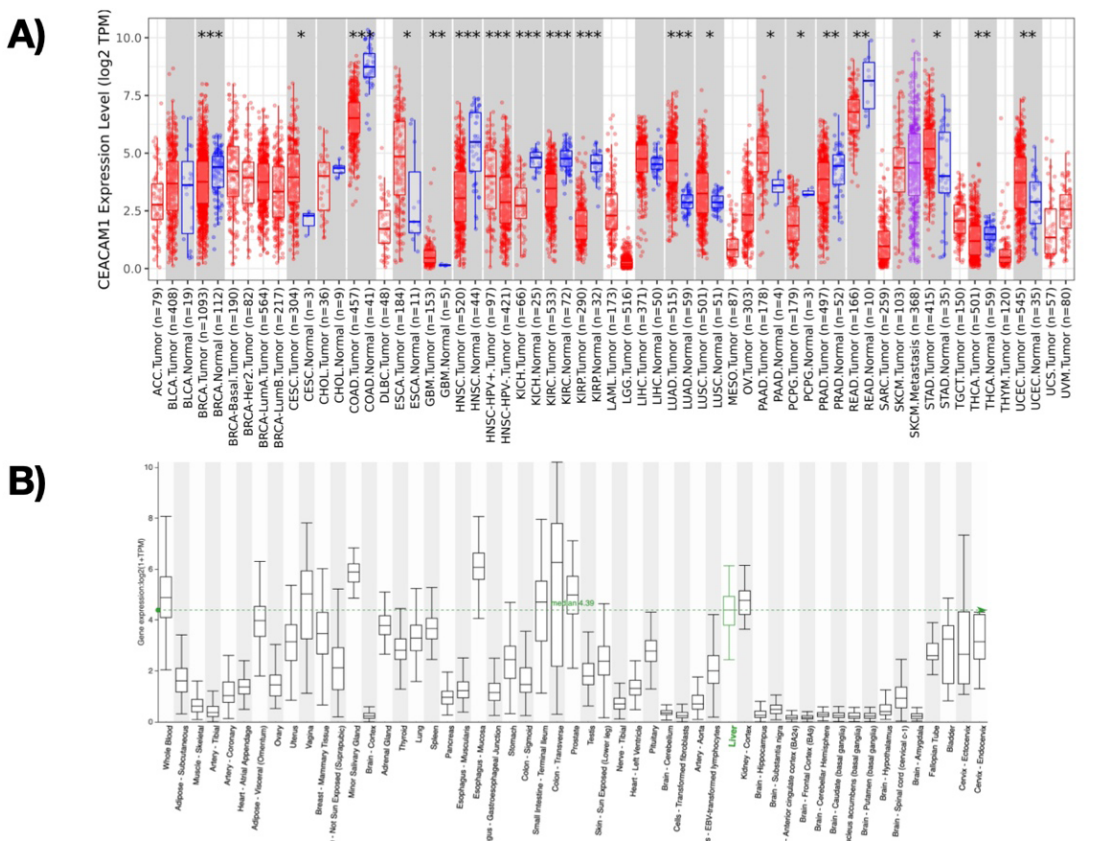

Figure 1. (A) *CEACAM1* mRNA expression profile in different human malignancies with normal control samples was analyzed. (B) *CEACAM1* expression in normal tissue samples was analyzed. *P<0.5, ** P<0.01, ***P<0.001.

RESULTS

The expression of *CEACAM1* in human malignancies and healthy samples.

To perform systematic characterization for *CEACAM1* expression in human malignancies with their associated normal counterparts, TIMER2.0 was utilized. *CEACAM1* expression was found to be upregulated in GBM, LUAD, LUSC, PAAD, STAD, TCHA and UCEC samples when compared to healthy samples (Figure 1A). Moreover, to evaluate *CEACAM1* expression in normal tissue samples, HCCDB database, providing the information from GTEx platform, was used. The analysis performed using the HCCDB database demonstrated that *CEACAM1* was mostly expressed in esophagus mucus, minor salivary gland, colon transvers, prostate, and kidney cortex (Figure 1B). Taken together, these findings indicate that *CEACAM1* mRNA expression was upregulated in different malignancies and expressed in normal tissue samples.

*C*EACAM1 is correlated with COVID-19 genes, *ACE2* and *TMPRSS2*.

ACE2 and *TMPRSS2* were two prominent proteins that were reported to play significant roles in facilitating viral entry and associated with increased COVID-19 susceptibility seen in cancer patients [4, 5, 20]. To investigate whether *CEACAM1* expression might be associated with *ACE2* or *TMPRSS2*, correlation analysis in TGCA samples was performed. For this purpose, TIMER2.0 database utilized whereby the expression of *CEACAM1* gene was assessed against *ACE2* and *TMPRSS2* expression in different malignancies. Based on the correlation analysis, *CEACAM1* was positively correlated with *ACE2* and *TMPRSS2* in most of the TCGA samples (Figure 2A). This result was further corroborated by visualizing the top four positively correlated tumor samples between *CEACAM1* and ***ACE2***, *TMPRSS2*, respectively. The expression of *CEACAM1* was positively correlated with *ACE2* in COAD (rho=0.423, p=2.24e=21), KIRC (rho=0.469, p=1.64e-30), UCEC (rho=0.47, p=4.16e-23), and OV (rho=0.474, p=2.36-e18) (Figure 2B). In addition, *CEACAM1* expression was found to be positively correlated with *TMPRSS2* in CESC (rho=0.593, p=2.1e-30), ESCA (rho=0.735, p=1.1e-32), HNSC (rho=0.672, p=7.38e-70), PAAD (rho=0.51, p=2.9e-13) (Figure 2C). The additional list of TGCA samples where the positive correlation between *CEACAM1* and ***ACE2***, *TMPRSS2* observed were shown as following: with ***ACE2***, ACC (rho=0.407, p=1.97e-04), KICH (rho=0.399, p=9.11e-04), CESC (rho=0.396, p=6.46e-13), ESCA (rho=0.384, p=6.65e-08) (Supplementary Figure 1A); with *TMPRSS2*, LUSC (rho=0.497, p=1.47e-32), READ (rho=0.494, p=1.34e-11), COAD (rho=0.415, p=1.71e-20), CESC (rho=0.593, p=2.1e-30) (Supplementary Figure 1B). Taken together, these results indicate that *CEACAM1*

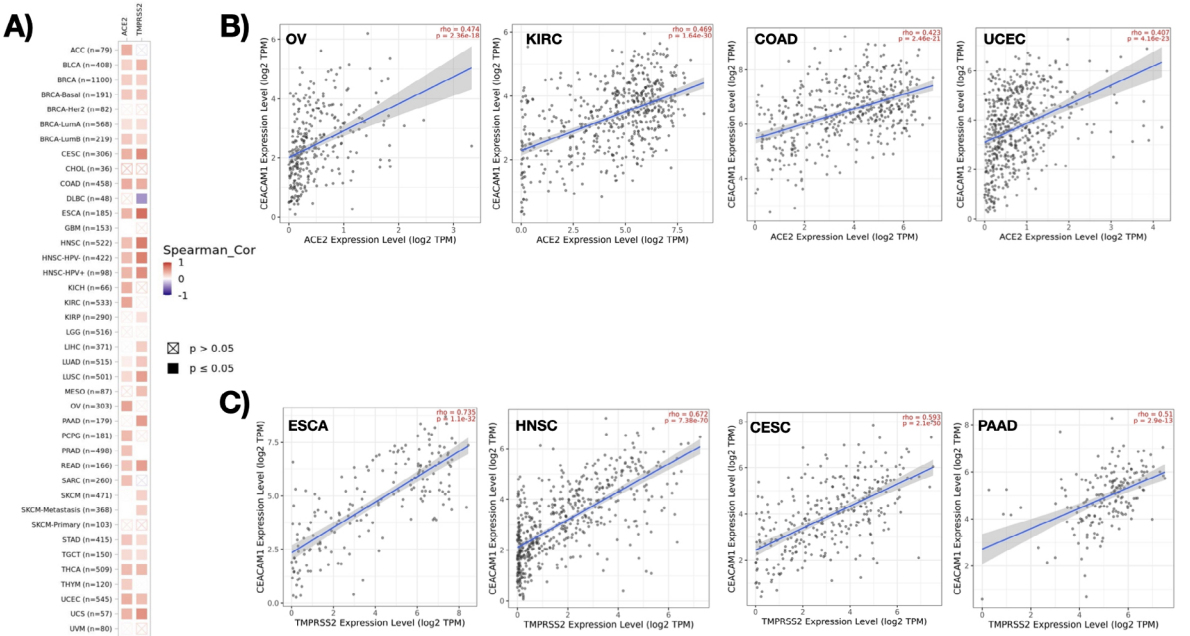

Figure 2. (A) Correlation analysis between *CEACAM1* and ACE2, *TMPRSS2* genes in different human malignancies, positive correlation when p\le0.05, p>0; and negative correlation when p\le0.05, p<0. Scatter plots show correlation analysis between *CEACAM1* and ACE2, *TMPRSS2* (B) in CAOD, KIRC UCEC, OV and (C) in CESC, ESCA, HNSC, PAAD samples.

expression is positively correlated with COVID-19 genes *ACE2* and *TMPRSS2* in malignancies, suggesting a potential participation of *CEACAM1* in increased COVID-19 susceptibility in cancer patients.

Single-cell RNA sequencing analysis revealed the upregulation of *CEACAM1* expression in squamous epithelial cells of COVID-19 positive patients.

To gain a better insight about the involvement of *CEACAM1* in COVID-19 disease, recently performed scRNA-seq data was utilized [33]. The scRNAseq approach enabled to understand the expression of *CEACAM1* in individual cells rather than its expression obtained using bulk tissue samples. This study applied multi-omics approach to assess COVID-19 related genomic alterations at the single-cell level [33]. To assess *CEACAM1* gene expression changes in COVID-19 groups in comparison to normal individuals, UCSC cell browser was used. The analysis showed that *CEACAM1* expression was upregulated in squamous epithelial cells in COVID-19 positive groups in comparison to normal individuals (Figure 3). This observation indicated that *CEACAM1* may therefore involve in modulating COVID-19 especially in squamous epithelial cells within the lung tissue and it requires further investigation to understand why specifically this group of cells within the lung organ express higher levels of *CEACAM1*.

Prognostic potential of *CEACAM1* in different malignancies.

To assess the expression of *CEACAM1* in survival of different human malignancies, TIMER2.0 database was used. The correlation in this database provides information about the outcome of gene expression on survival on specific cancers. The analysis performed using this database showed that increased expression of *CEACAM1* in LGG (z score=9.358) and KIRP (z score=2.251) was linked with poor prognosis in the survival of these patients (Figure 4A). Moreover, the Kaplan-Meir analysis for overall survival demonstrated that elevated *CEACAM1* expression levels were significantly correlated in LGG and KIRP patients (Figure 4B and 4C). These findings suggest a prognostic role of increased *CEACAM1* expression in LGG and KIRP malignancies. *CEACAM1* expression enabling prognostic function distinctly only in LGG and KIRP malignancies can be reasoned due to the scale of dataset, and hence bigger cohorts for validation and investigation would be required.

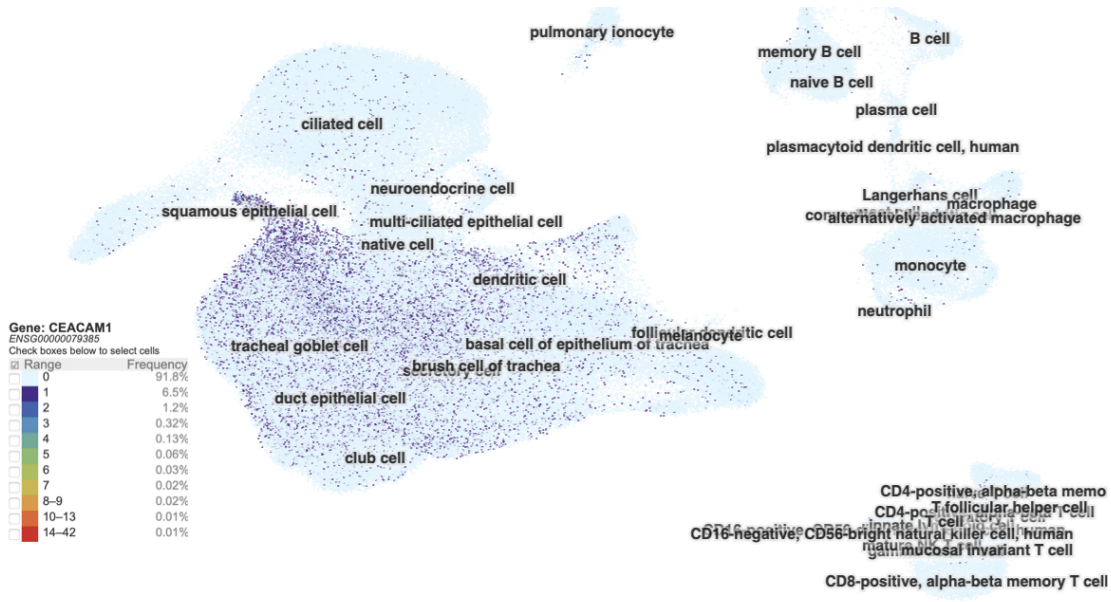

Figure 3. Single cell RNA expression levels of *CEACAM1* gene in individual airway cells of COVID-19 patients were shown. Blue to red gradient indicate an increased range of gene expression levels with associated frequencies.

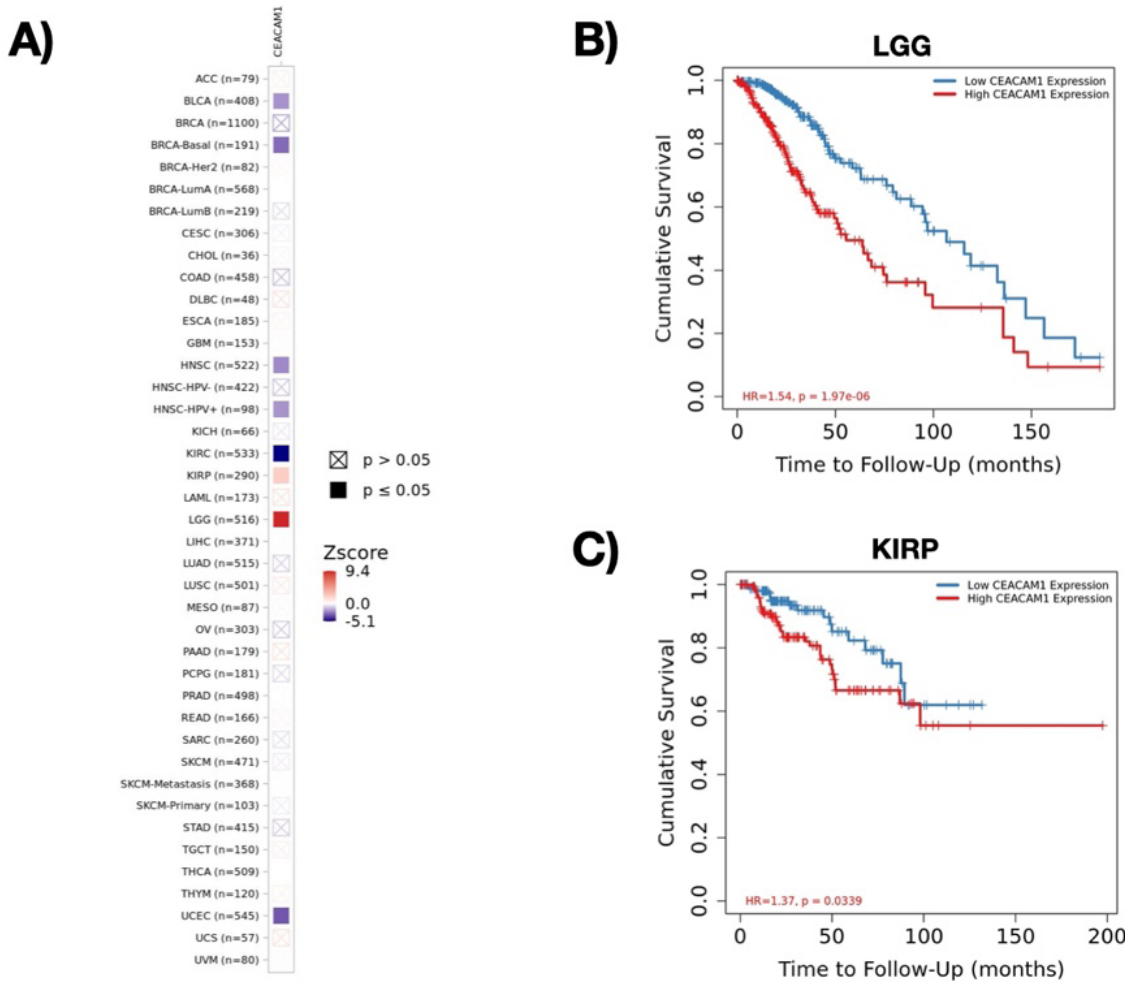

Figure 4. (A) The association of *CEACAM1* expression with the survival in different human malignancies was shown. Kaplan-Meier plots demonstrating the overall survival based on *CEACAM1* expression levels in (B) LGG and (C) KIRP.

***CEACAM1* expression is associated with *HAVCR2*.**

To investigate the physical interaction and co-expression of *CEACAM1* with potential candidates, GENEMANIA webtool was used. The analysis performed using the webtool demonstrated a list of hits interacting and co-expressing with *CEACAM1* such as ***HAVCR2, ITGA5, CEACAM8, CEACAM3, FN1, SP2, CEACAM6, SOX9, ITGB1, CEACAM7, ITGB3, FASN, CEACAM5, CLEC4M, ANXA2, CD209, CEP57, SHC1, CARTPT, SLC26A3*** (Figure 5A). Among the long list of interactors with *CEACAM1*, ***HAVCR2*** (Hepatitis A virus cellular receptor 2) was listed on the top with its strong association with *CEACAM1*. Therefore, ***HAVCR2*** was selected to investigate its potential association with *CEACAM1*. The correlation analysis between *CEACAM1* and ***HAVCR2*** in different TCGA samples was performed using TIMER2.0 database. This analysis showed that *CEACAM1* and *HAVCR2* are positively correlated in nearly half of TCGA samples (Figure 5A). To visualize the correlation analysis results between *CEACAM1* and ***HAVCR2***, individual correlation plots were generated for the top three correlation coefficient scores obtained in different malignancies. These included GBM (rho=0.46, p=2.3e-09), KICH (rho=0.374, p=1.97e-03), LGG (rho=0.373, p=1.71e-18) (Figure 5C, 5D, and 5E). Taken together, these findings indicated that *CEACAM1* exhibited strong interaction with *HAVCR2*, based on results obtained from a gene network analysis tool. In addition, a significant positive correlation detected between the expression levels of *CEACAM1* and ***HAVCR2*** particularly in GBM, KICH and LGG malignancies suggest a shared mechanism between these two genes for a specific function.

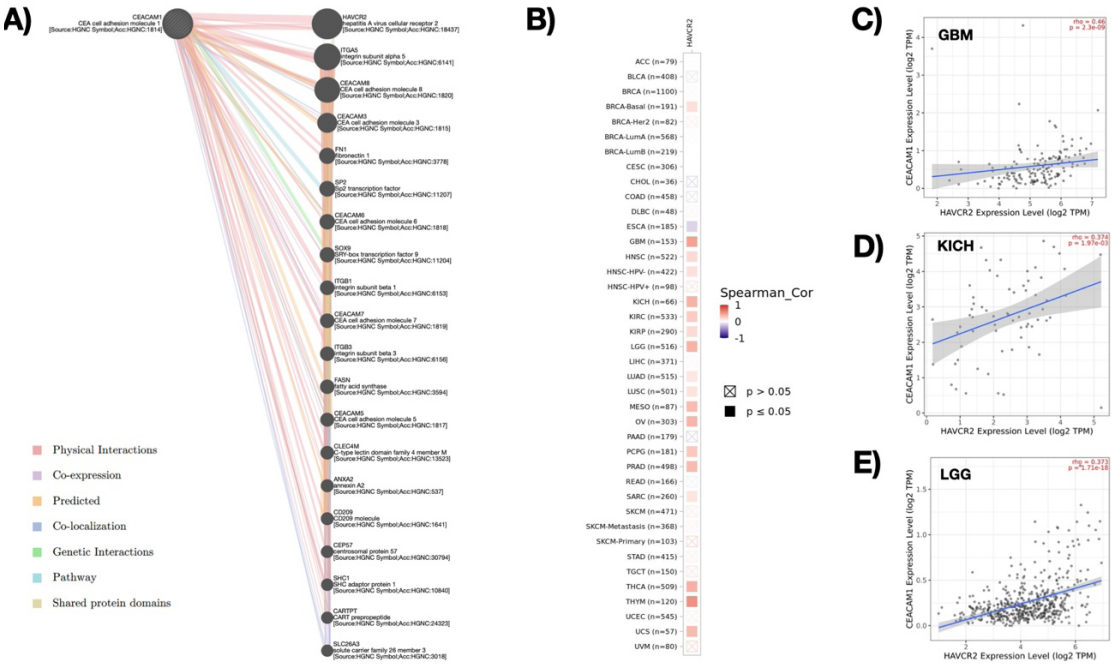

Figure 5. (A) Gene network analysis of *CEACAM1* with its physical interactors, co-expressing partners, predicted features, co-localized, genetic interactors, pathways, and shared protein domains were presented. (B) Correlation analysis between *CEACAM1* and *HAVCR2* genes in different human malignancies, spearman's p (red): positive correlation p\le0.05, p>0; spearman's p (blue): negative correlation p\le0.05, p<0. Scatter plots show the correlation analysis between *CEACAM1* and *HAVCR2* (C) in GBM, (D) in KICH, and (E) in LGG samples.

The correlation of *HAVCR2* expression with *ACE2* and *TMPRSS2*.

Since *CEACAM1* and *HAVCR2* was found to be interacting and there was a significant positive correlation between these two genes in different malignancies, we next aimed to determine whether there could be an association between *HAVCR2* and SARS-CoV-2 infection genes. To address this question, TIMER2.0 database was used to assess correlation coefficient between *HAVCR2* and SARS-CoV-2 infection genes, *ACE2* and *TMPRSS2*. This analysis demonstrated that there was a positive correlation between *HAVCR2* and *ACE2* in a number of malignancies including KIRC, KIRP, PAAD PRAD UCEC, UCS (Figure 6A). In addition, the same analysis demonstrated a positive correlation between *HAVCR2* and *TMPRSS2* in LGG, LUSC, THCA, and UCS (Figure 6B). The top three strongest correlation coefficient observed between *HAVCR2* and *ACE2* genes were as following: KIRC (rho=0.355, p=2.86e-17) KIRP (rho=0.38, p=2.07e-11) and PRAD (rho=0.403, p=7.38e-21) (Figure 6B). Moreover, the top three strongest correlation detected between ***HAVCR2*** and *ACE2* genes were as following: LUSC (rho=0.256, p=5.76e-09), THCA (rho=0.261, p=2.2e-09), UCS (rho=0.281, p=3.42e-02) (Figure 6C). Furthermore, the expression of *HAVCR2* gene was investigated in different human malignancies using TIMER2.0 database and *HAVCR2* levels were upregulated in CESC, CHOL, ESCA, GBM, HNSC, KIRC, KIRP, LUAD, LUSC, STAD, THCA, and UCEC samples relative their normal counterparts (Supplementary Figure 2). Collectively, these results indicate that *HAVCR2* might be involved in modulating elevated risk for COVID-19 in cancer patients.

Prognostic potential of *HAVCR2* in different malignancies.

Lastly, prognostic potential of ***HAVCR2*** expression in different malignancies were investigated. TIMER2.0 database providing an information in relation to expression of ***HAVCR2*** and overall survival was utilized. This analysis showed that increased ***HAVCR2*** expression in LGG (z score=4.262), LAML (z score=2.045), THYM (z score=3.075), UVM (z score=2.705) and TGCT (z score=2.128) were linked to poor prognosis of the patients (Figure 7A). Furthermore, ***HAVCR2*** expression were significantly correlated in LGG and KIRP patients as assessed by the Kaplan-Meir analysis for overall survival (Figure 7B and 7C). These findings indicated that elevated ***HAVCR2*** might be linked to poor prognosis in overall survival in certain malignancies.

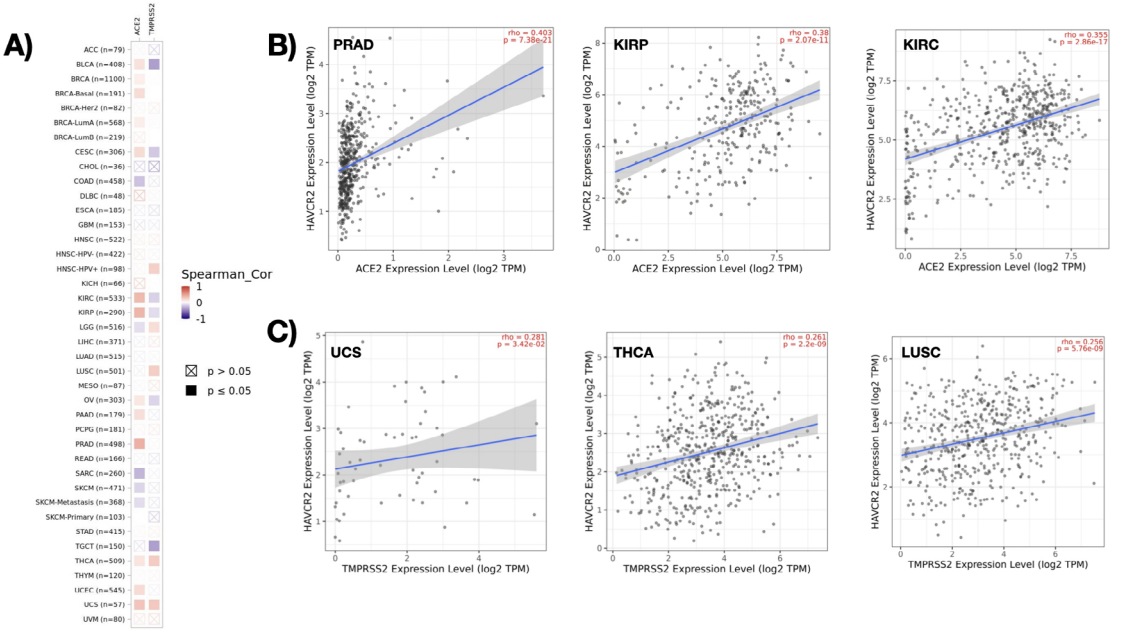

Figure 6. (A) Correlation analysis between *HAVCR2* and ACE2, *TMPRSS2* genes in different human malignancies. Scatter plots show correlation analysis between *CEACAM1* and ACE2, *TMPRSS2* (B) in KIRC, KIRP PRAD, and (C) in LUSC, THCA, UCS samples.

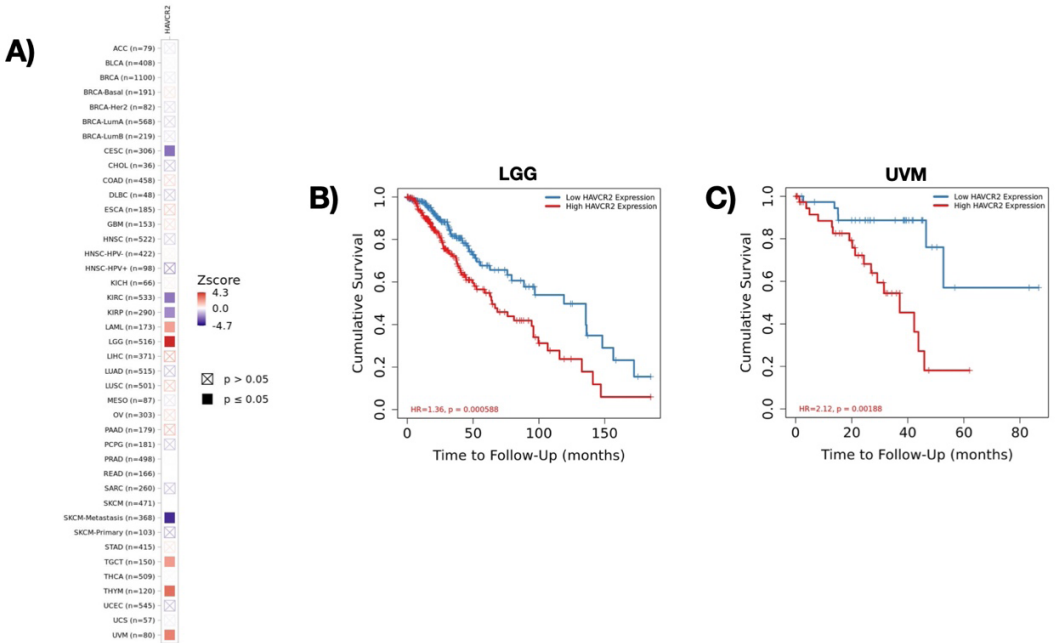

Figure 7. (A) The association of *HAVCR2* with the survival in different human malignancies was demonstrated. Kaplan-Meier plots demonstrating the overall survival based on *HAVCR2* expression levels in (B) LGG and (C) UVM.

DISCUSSION

The COVID-19 has caused a tremendous research effort to understand underlying mechanisms of the infection and casual links with different diseases [3]. Cancer is one of diseases often associated with impaired immunity and studies showed that cancer patients might be more prone to COVID-19 compared with healthy population [7–10]. A number of studies demonstrated elevated levels of *ACE2* and *TMPRSS2* in different malignancies, suggesting common underlying mechanisms in both diseases [1, 5, 19, 35]. Another common pathway activated both in cancer and COVID-19 disease is inflammation [36]. Inflammatory nature of both diseases results in secretion various cytokines and chemokines such as IL-6, TNF-α and IL-1β which is often associated with the severity of these diseases.

CEACAM1 was previously shown to participate in immune exhaustion whereby negatively regulating T-cell receptor signaling [21]. Due to this function, *CEACAM1*, alongside with additional proteins, are considered as inhibitory receptors (IRs) [37]. During the early phases of COVID-19, anti-viral interferon type I signaling was silenced to promote to viral propagation and infection seen at later phases [38]. In COVID-19, considered as a chronic viral infection, the IRs were upregulated whereby elimination of viral load is delayed [25, 39]. This is in fact seen as one of the mechanisms facilitated by IRs including *CEACAM1* in SARS-CoV-2 infection for immune suppression and evasion [24, 25]. Considering impaired immune system associated with cancer, our results suggest the role of elevated *CEACAM1* in different malignancies and its association with COVID-19 genes *ACE2* and *TMPRSS2* might contribute to explain why cancer patients can be more prone to COVID-19.

As *CEACAM1* regulates viral evasion as being part of the inhibitory receptors, *CEACAM1* was also considered as a plausible target in cancer immunotherapy [29, 40]. Immune modulatory approaches based on activating immune cells to attack on cancer cells form the basis of cancer immunotherapy [41]. As an example, PD-1 and CTLA-4 were broadly studied cancer immunotherapy and chronic infections [42]. Similar to cancer therapy approaches, aiming to target PD-1 and CTLA-4, inhibition of *CEACAM1* may therefore result in suppression of inhibitory feedback mechanism to activate impaired immune system in cancer patients and hence the increased risk to COVID-19.

Similar to *CEACAM1*, *HAVCR2* (also known as TIM-3) is known as another critical inhibitory receptor and it was reported to involve in COVID-19 by upregulation the *HAVCR2* expression in a subset of T cells in COVID-19 patients [21, 43, 44]. Exhaustion of T cells is one of the critical aspects of COVID-19 infection as it often results in inability of immune cells to react to viral infection [45]. Therefore, finding an association between *HAVCR2* and SARS-CoV-2 infection genes in different malignancies, as part of this study, supports the earlier findings about the involvement *HAVCR2* in COVID-19 disease and further provides evidence for potential link for increased susceptibility of this viral infection in cancer patients. In this context, inhibition of *HAVCR2* in different types of cancer model systems were studied and studies concluded *HAVCR2* as a critical player in mediating immune evasion and tumor progression [43, 46–51]. For example, increased *HAVCR2* expression in colon cancer samples exhibited restriction on T-cell response and activation of immune escape mechanisms, suggesting HACVR2 as a strong candidate for targeting to restore impaired immune function [43, 50]. Alongside these observations and our findings, *HAVCR2* can potentially be thought as good intervention in cancer patients developing COVID-19 to silence and suppress viral infection and propagation.

Taken together, in this study, it was shown that *CEACAM1* might be involved in providing increased susceptibility to COVID-19 disease in cancer patients based on: 1) *CEACAM1* was upregulated in different malignancies compared to healthy samples, 2) *CEACAM1* was positively correlated with SARS-CoV-2 infection genes *ACE2* and *TMPRSS2*, 3) increased *CEACAM1* expression was detected in squamous epithelial cells in lung alveolar tissue samples of COVID-19 positive patients in comparison to healthy individuals, 4) *CEACAM1* was associated with *HAVCR2* and *HAVCR2* was positively correlated with *ACE2* and *TMPRSS2* in different malignancies. Given the supporting evidence on the inhibitory role of *CEACAM1* and *HAVCR2* in providing impaired immune system both in cancer and COVID-19 diseases, increased expression levels of these two genes alongside with SARS-CoV-2 infection genes *ACE2* and *TMPRSS2* might provide an explanation for cancer patients as being more prone to COVID-19 disease.

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