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Association of ACE and ACE2 Genes Elevate the Risk of Lung Cancer

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Abstract

Background: ACE and ACE2 are biologically potential biomarkers responsible for the production and progression of lung cancer. We aimed to analyzed the expression and association of ACE and ACE2 genes in lung cancer & Covid-19.

Subjects and methods: Web-based bioinformatics tools were used to assess the association of ACE and ACE2 with lung cancer risks. The prognostic significance of mRNA expression of ACE and ACE2 in lung cancer were evaluated using the Kaplan–Meier plotter. Univariate and multivariate Cox proportional hazards regression analysis were performed to determine whether ACE and ACE2 are an independent risk factor for overall survival (OS) and fast progression (FP) of lung cancer patients. Additionally, STRING database was used to analyze protein-protein interactions.

Result: Our data confirmed that ACE is significantly expressed and associated with higher lung cancer risks where ACE2 role in developing lung cancer is controversial but in Covid-19. Moreover, high expression of ACE and ACE2 might predict poor OS and FP in lung cancer patients. Besides, disease stage and expression level of ACE and ACE2 were correlated with fast progression and overall survival in lung cancer. Both ACE and ACE2 were found highly co-expressed with different immune checkpoints. Analysis of protein-protein interaction based on STRING database gained top 10 genes which could interact with ACE and ACE2.

Keywords: Lung cancer; Lung Adenocarcinoma (LUAD); Lung squamous cell carcinoma (LUSC); ACE and ACE2.

Introduction

Lung cancer is the most common reason for cancer-related death globally [1]. More than half of the lung cancer patients are diagnosed at a distant stage, with a 5-year overall survival (OS) rate of 18% [2]. It is the most prevalent malignant tumor in the majority of nations and the leading cause of cancer-related death in both sexes worldwide. Tobacco use, the principal etiological factor in lung carcinogenesis, greatly influences the regional and temporal patterns of lung cancer incidence as well as lung cancer mortality on a population level . The descriptive epidemiology of lung cancer may be shaped by additional factors such as genetic vulnerability, poor diet, occupational exposures, and air pollution, either alone or in combination with cigarette use . Currently, more men than women die from lung cancer each year, although in developed nations, lung cancer mortality among women has recently increased rapidly, while it has leveled off or decreased among men . While the impact of cigarette smoking has been determined to be the primary cause of lung cancer among women in the majority of developed countries, various types of epidemiological research have revealed a discernible role for some other factors that either act independently as risk factors or interact with the impact of smoking . The current TNM staging system is widely used as guidance to select initial treatment and evaluate prognosis of patients. However, as high as 40% of lung cancer patients at early TNM stage suffer from relapse after surgical resection, suggesting that additional molecular markers in combination with TNM staging system are urgently needed for the prognosis of patients with lung cancer. Among having large number of factors to develop lung cancer, recently it has been notified that, the two enzymes named ACE & ACE2 might have the association to develop lung cancer. However, the roles of ACE with high homology to ACE2, in lung cancer and COVID-19 have not been entirely clarified.

In the renin-angiotensin system (RAS), angiotensin converting enzyme, a zinc-containing dipeptidase, is essential for controlling circulatory homeostasis as well as the pathophysiology of carcinomas [3]. The expression of ACE is up-regulated in numerous malignancies with functions for angiogenesis, tumor cell proliferation and migration, and metastatic behavior, according to newly available information [3,4]. Studies conducted both in vivo and in vitro showed that reducing ACE activity reduced tumor growth and angiogenesis [5] and regular ACE inhibitor use may lower the chance of getting cancer, especially colorectal cancer (CRC) [6,7]. At the moment, ACE inhibitors are thought to be used as cutting-edge cancer preventive and antineoplastic therapy [7]. The *ACE* gene is located on chromosome 17q23 and consists of 26 exons and 25 introns in humans. Numerous research have previously been conducted to look at the relationship between the ACE and risk of different malignancies in different populations, including breast cancer, prostate cancer, oral cancer, renal cancer, lung cancer, gastric cancer.

Angiotensin-converting enzyme 2 (ACE2), a recently discovered RAS component, shares 42% of its amino acid sequences with ACE [8] . Angiotensin II is transformed by ACE2 into angiotensin-(1–7), which is its primary function. Angiotensin-(1-7) has a higher level of concentration in lung serum in lung cancer, and ACE2 inhibitors increased lung cancer cell death in human and rat alveolar epithelial

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cells. Consequently, strengthen the link between SARS-CoV-2 infection and lung cancer. Lack of ACE2 expression is a sign of poor lung function since it indicates increased lung edema, neutrophil infiltration, and decreased vascular permeability, all of which increase the risk of SARS-CoV-2 infection [9]. Maintaining ACE2 levels increases patient survival in lung cancer cases; enzymatic activity causes an inflammatory storm that, by preventing gas exchange between alveoli and capillaries, aids in the removal of SARS-CoV-2 from the lung. Increased or unchecked ACE2 expression in combination with S protein increases the risk of SARS-CoV-2 infection [9,10]. The potential biomarker and treatment target for SARS-CoV-2 infection has been identified as ACE2. Other functions of ACE2 include inhibiting the angiogenesis system and promoting the development of malignant cells. It functions as a contra-regulator of the renin-angiotensin system. It interferes with the actions of angiotensin-II (Ang II) and the structurally related receptor ACE, adversely affecting inflammation, cell proliferation, and vasoconstriction. The membrane-bound angiotensin-converting enzyme-2 (ACE-2) functions as an entrance receptor and is a crucial host protein for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Wan, Shang et al. 2020). In the respiratory system, low quantities of ACE2 mRNA can often be found at the transcriptional level. Studies have revealed greater ACE2 mRNA levels in patients' nasal swabs, bronchial brushes, and bronchoalveolar lavages when they had COVID-19 illness (Chua, Lukassen et al. 2020, Ortiz, Thurman et al. 2020). One of the computational analyses recently uncovered that, ACE2 is vitally involved with both COVID-19 and lung cancer.

Recently, researchers looked at the correlation between the transcriptional levels of ACEs and the clinicopathological characteristics of individuals with lung cancer. Their findings demonstrated that ACE was considerably expressed differently in nodal metastasis, smoking behavior, and histological subtypes of LUAD patients as well as LUSC patients. In addition to the age, TP53 mutation status, histological subtypes, and smoking habits of LUAD, ACE2 expression was also significantly varied in the histological subtypes, smoking habits, and individual cancer stage of LUSC patients. They also discovered that the mRNA expression levels of the majority of the ACEs family members had a significant impact on the prognosis of lung cancer patients (Wan, Shang et al. 2020). High expression levels of the mRNAs for ACE, ACE2, and TMEM27 specifically indicated that lung cancer patients will have higher overall survival. A favourable initial advancement of lung cancer patients was connected with higher mRNA expression of ACE and ACE2. Patients with lung cancer who had upregulated ACE2 had good post-progression survival. Only ACE2 has the capacity to independently affect a patient's prognosis for lung cancer in the independent prognostic analysis for ACEs. There is no such type of research concerning the ACE and ACE2 correlation with lung cancer and covid-19 carried. Here we investigated the expression, correlation and survival analysis of both ACE and ACE2 with LUAD and LUSC risks and covid-19 development and severity as well by using the publicly available computational biology tools. Therefore, this study aims to disclose the risk of lung cancer and covid-19 associated with ACE and ACE2 expression.

Material and methods

Analysis of gene expression and immune infiltration profile with TCGA cancer data.

TIMER2.0 allows the visualization of the immune infiltration levels for The Cancer Genome Atlas (TCGA), which provides comprehensive analysis and visualization functions of tumor infiltrating immune cells. Gene_DE module in TIMER2.0 allows the study of differential expression between tumor and adjacent normal tissues for any gene of interest across all TCGA tumors. Several types of cancer and normal data available in the TCGA cancer data set.

Assessment of ACE and ACE2 expression and correlation level.

The gene expression data cohort with Lung cancer was measured using Gene Expression Profiling Interactive analysis (GEPIA2) online tool, a recently developed interactive database for analysing the expression and correlation of genes in TCGA data.

Survival Analysis

The prognostic significance of mRNA expression of ACE and ACE2 in lung cancer were evaluated using the Kaplan–Meier plotter, an online database including gene expression data and clinical data (Győrffy, Surowiak et al. 2013). The overall survival (OS) and the fast progression (FP) were collected in lung cancer database. Briefly, the genes ACE and ACE2 were uploaded into the database, and samples were divided into two cohorts according to the median expression of ACE and ACE2 (high vs low expression) to obtain the Kaplan–Meier survival plots, in which the number-at-risk were shown below the main plot. Log-rank P-value and hazard ratio (HR) with 95% confidence intervals were calculated and displayed on the web page. The p values <0.05 were considered statistically significant. In this study, "array quality control" was selected to "exclude biased arrays".

Protein–protein interaction network construction

The Search Tool for the Retrieval of Interacting Genes (STRING) database aims to construct functional protein association networks by consolidating known and predicted protein–protein association data for a large number of organisms (Szklarczyk, Morris et al. 2017). The STRING resource is available at http://string-db.org/. The corresponding protein–protein interaction network of ACE and ACE2 were constructed when we selected the interactions pertaining to Homo sapiens and showed minimum interactions with a confidence score 0.9.

Statistical analysis

The significance denoted by ns: not significant; *: p-value < 0.05; **: p-value <0.01; ***: p-value <0.001. Log-rank P-value and hazard ratio (HR) with 95% confidence intervals were calculated and the p values < 0.05 were considered statistically significant.

Result

ACE and ACE2 genes expression with different TCGA cancer data

We analyzed the expression of ACE and ACE2 genes with differential expression between tumor and adjacent normal tissues across all TCGA tumors utilising the Gene_DE module in TIMER2.0 tool. The statistical significance was calculated by the Wilcoxon test noted by the number of stars (*: p-value < 0.05; **: p-value <0.01; ***: p-value <0.001). It can identify genes that are up-regulated or down-regulated in the tumors compared to normal tissues for each cancer type, as displayed in gray columns when normal data are available. After proper analyzing, we found that ACE gene expression were statistically significant with the development and progression of both lung adenocarcinoma (LUAD) and Lung squamous cell carcinoma (LUSC) and ACE2 gene expression was statistically significant with the development and progression of LUAD but not LUSC (Figure 1A and Figure 1B).

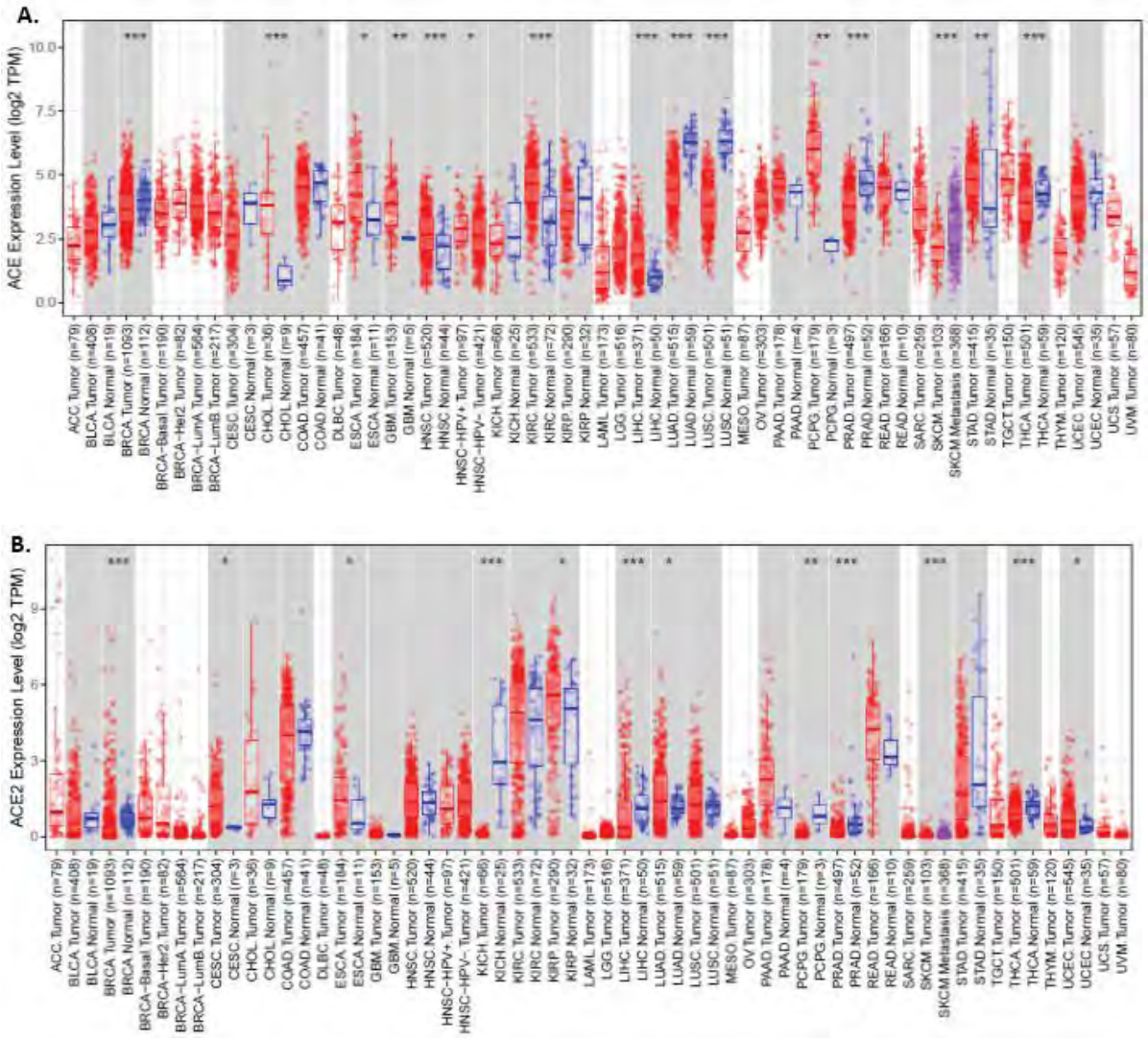

Figure 1: Visualizing the expression of ACE and ACE2 with different TCGA cancer data.

Gene_DE module in TIMER2.0 allows studying the differential expression between tumor and adjacent normal tissues for any gene of interest across all TCGA tumors. Distributions of gene expression levels are displayed using box plots for ACE **(A)** and for ACE2 **(B)**. The statistical significance computed by the Wilcoxon test is annotated by the number of stars (*: p-value < 0.05; **: p-value <0.01; ***: p-value <0.001). It can identify genes that are up-regulated or down-regulated in the tumors compared to normal tissues for each cancer type, as displayed in gray columns when normal data are available.

ACE and ACE2 expression and correlation with lung cancer

ACE and ACE2 gene expression were analyzed using GEPIA2 online tool and it was found that the ACE gene expression was significantly expressed with LUAD and LUSC progression in TCGA datasets (Figure 2A), whereas, ACE2 gene expression was not significantly expressed with LUAD and LUSC progression in TCGA datasets (Figure 2B). ACE and ACE2 genes expression were also positively correlated both in the LUAD (R= 0.067) and LUSC in TCGA dataset using Spearman's correlation (R= 0.0019) (Figure 3A and Figure 3B).

Clinical outcome of ACE and ACE2 with Lung cancer

We explored the prognostic value of the expression of ACE and ACE2 using Kaplan–Meier plotter (www.kmplot.com). The desired Affymetrix ID was valid: 227463_at (ACE) for Overall survival (OS). A low expression of ACE mRNA was related to significantly shorter overall survival probability than high expression group for all lung cancer patients (n=1144, HR 0.74 [0.63– 0.87], P= 3e-04) (Figure 4A). Likewise, patients with low expression of ACE mRNA was related to shorter fast progression (FP) for all lung cancer patients (n= 596, HR 0.86 [0.65–1.12], P=0.26) (Figure 4B) and the result was not statistically significant. In case of ACE2, patient's with high expression of ACE2 mRNA was related to significantly shorter overall survival probability for all lung cancer patients (n=1925, HR 0.87 [0.77–0.99], P=0.029) (Figure 4C), whereas, patient's low expression of ACE2 mRNA was related to shorter fast progression (FP) for all lung cancer patients (n=982, HR 0.87 [0.72–1.05], P=0.15) (Figure 4D) and the result was not statistically significant.

ACE and ACE2 expression with different pathological stages of lung cancer

We then checked the expression pattern of ACE and ACE2 in lung cancer pathological stages and found that the expression was significantly different between the ACE and ACE2 in TCGA lung cancer (Figure 5A and Figure 5B)

Correlation of gene expression with immune infiltration profile in lung cancer

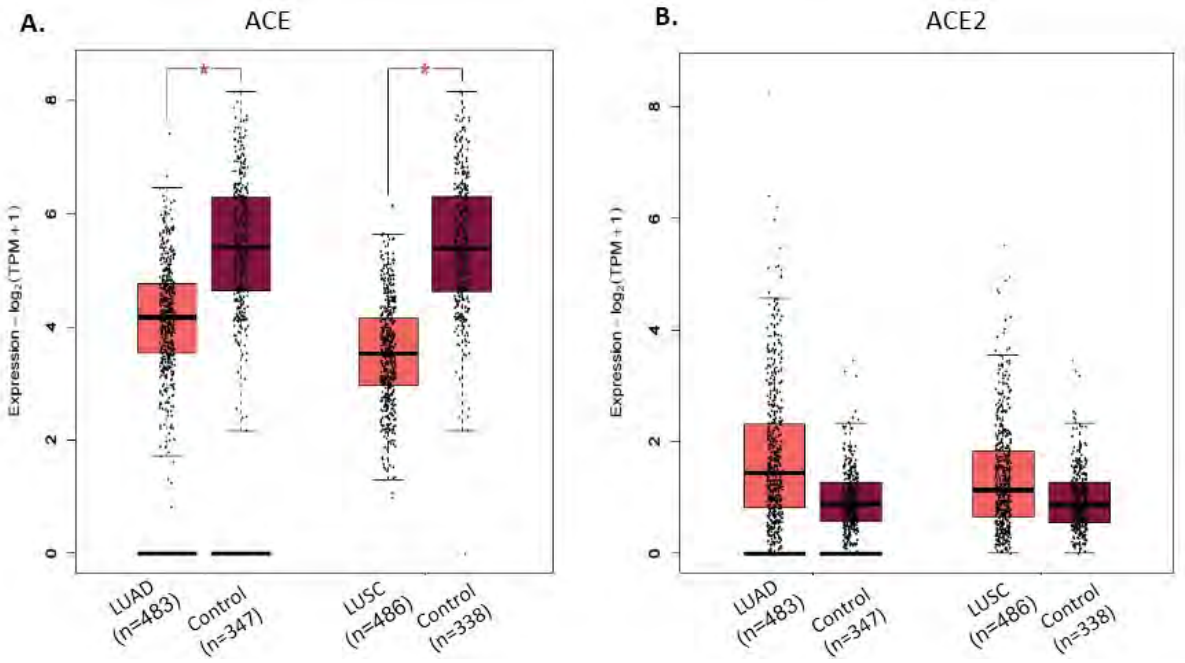

Figure 2: ACE and ACE2 expression with were analyzed using GEPIA2 online tool.

(A) ACE expression were significantly expressed both in lung Adeno Carcinoma (LUAD) and lung squamous cell carcinoma (LUSC) risks in TCGA datasets. **(B)** ACE2 expression were not significantly expressed both in lung Adeno Carcinoma (LUAD) and lung squamous cell carcinoma (LUSC) risks in TCGA datasets. The significance denoted by ns: not significant; *: p-value < 0.05; **: p-value <0.01; ***: p-value <0.001.

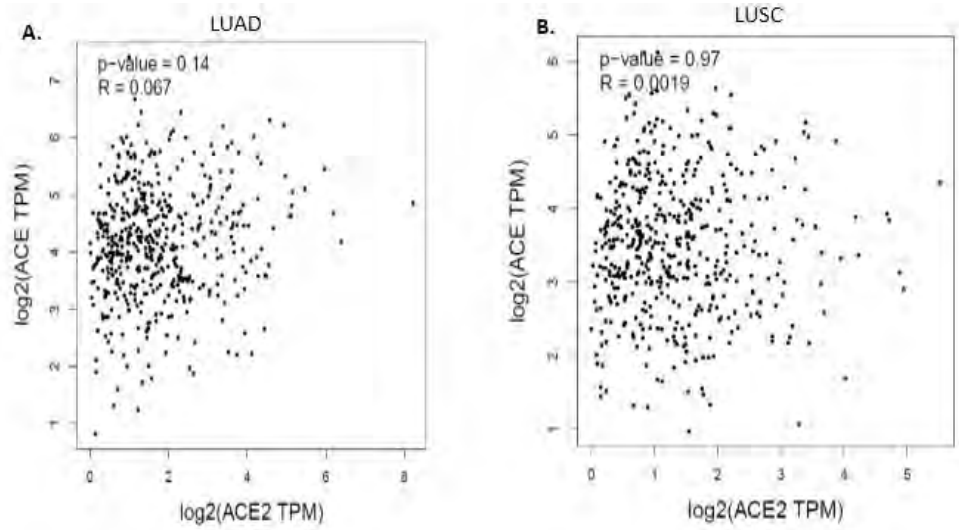

Figure 3: Correlation analysis between ACE and ACE2 genes in LUAD and LUSC.

(A, B) ACE and ACE2 gene expression were positively correlated in LUAD (R=0.067) and in LUSC (R=0.0019) using spearman correlation by plotting the Log2 of ACE transcript per million (TPN) versus Log2 of ACE2 transcript per million of TCGA cancer datasets. Data were analyzed using GEPIA2 online tool. The significance denoted by ns: not significant; *: p-value < 0.05; **: p-value <0.01; ***: p-value <0.001.

The correlation of ACE and ACE2 genes expression with immune infiltration profile in lung cancer were measured using the TIMER2.0 online tools. A scatter plot showed the Spearman's correlation in different immune cells. In case of ACE, CD8+ T cell (Figure 6A), mast cell activated (Figure 6B), macrophages M1 (Figure 6C), macrophages M2 (Figure 6D) showed positive correlation with ACE expression in LUAD in TCGA patient's sequencing data. It is also positively correlated with mast cell activated (Figure 6F), macrophages M1 (Figure 6G), macrophages M2 (Figure 6H) and negatively correlated with CD8+ T cell (Figure 6E) in LUSC patient's. In case of ACE2, CD8+ T cell (Figure 6I), macrophages M1 (Figure 6K) and macrophages M2 (Figure 6K) were negatively correlated with LUAD patient's, however, mast cell activated (Figure 6J) was positively correlated with LUAD patient's. It is also positively correlated with mast cell activated (Figure 6N), eosinophil (Figure 6O) and macrophages M1 (Figure 6P) and negatively correlated with T cell regulatory (Figure 6M) in LUSC patient's. And the result was statistically significant.

Interaction networks of ACE and ACE2.

In case of ACE: The STRING database was used to consolidate known and predicted protein–protein association with ACE. As shown in Figure 7A, the top 10 predicted functional partners were as follows:

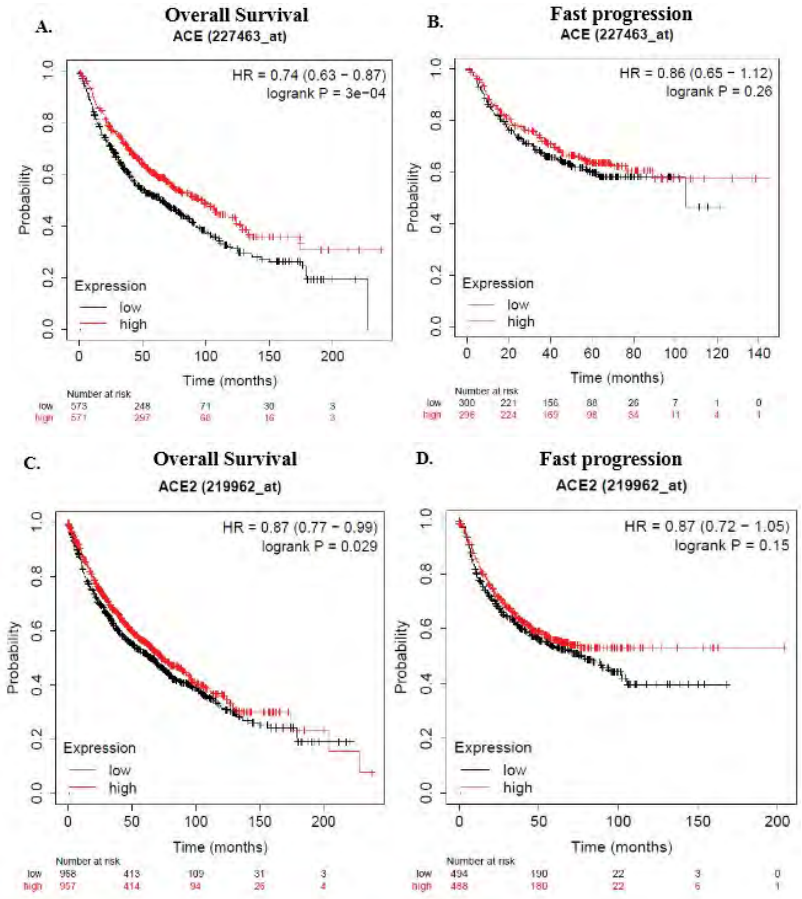

Figure 4: Association of ACE and ACE2 expression with clinical outcome.

Impact of ACE expression on survival curves were plotted. (A) Overall survival (OS) of all lung cancer patients (n=1,144) for ACE, (B) Fast progression (FP) with ACE expression (n= 596), (C) Overall survival (OS) of all lung cancer patients (n=1,925) for ACE2, (B) Fast progression (FP) with ACE2 expression (n= 982) Data were analyzed using Kaplan–Meier plotter (www.kmplot.com) on TCGA cancer datasets. CI, confidence interval; HR, hazard ratio. The significance denoted by ns: not significant; *: p-value < 0.05; **: p-value <0.01; ***: p-value <0.001

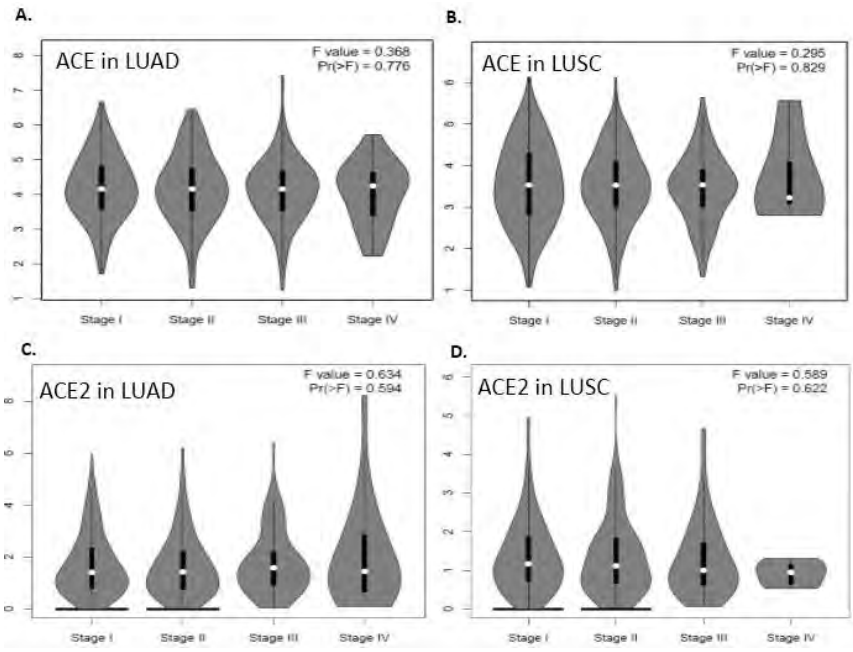

Figure 5: Expression of ACE and ACE2 with TCGA cancer data in GEPIA2 tool.

(A, B) Expression of ACE with different stages of LUAD and LUSC. (C, D) Expression of ACE2 with different stages of LUAD and LUSC. The significance denoted by ns: not significant; *: p-value < 0.05; **: p-value <0.01; ***: p-value <0.001.

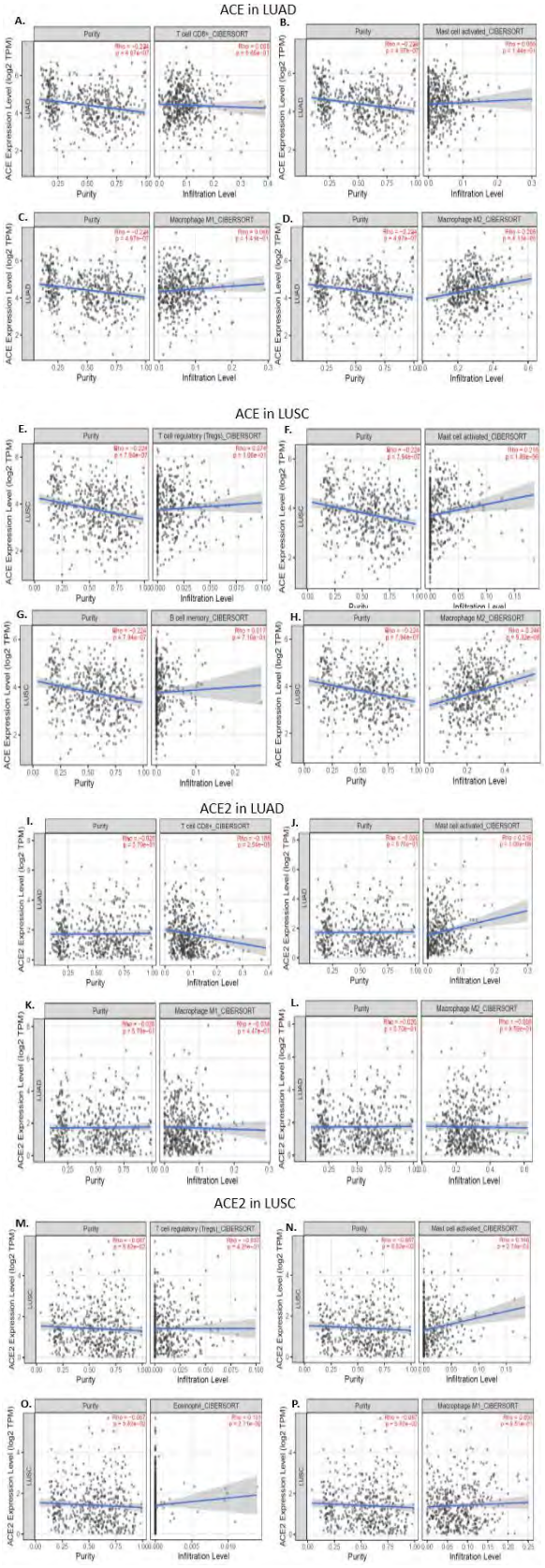

Figure 6: TIMER2.0 allows visualizing the expression with immune infiltration profile in lung cancer.

Scatter plot showed the spearman correlation in different immune cells. (**A, B, C, D, E, F, G and H**) The expression of ACE in LUAD and LUSC patient's sequencing data. **(I, J, K, L, M, N, O and P)** The expression of ACE2 in LUAD and LUSC patient's sequencing data. The *p* values < 0.05 were considered statistically significant using the TCGA breast cancer data cohort.

AGT (score =0.998), KNG1 (score =0.982), REN (score =0.967), RHOA (score =0.963), RHOC (score =0.932), ATTR1 (score =0.924), AGTR2 (score =0.916), BDKRB2 (score =0.878), MME (score =0.865) and NR3C2 (score =0.863). Function enrichment analysis against gene ontology in this network showed that for biological processes, this network is most enriched in cell division, small GTPase-mediated signal transduction and chromosome segregation. The STRING database was used to consolidate known and predicted protein–protein association with ACE2. As shown in Figure 7B, the top 10 predicted functional partners were as follows: SLC6A19 (score =0.999), AGT (score =0.998), DPP4 (score =0.980), REN (score =0.966), MME (score =0.960), PRCP (score =0.929), MEPIA (score =0.925), SLC1A7 (score =0.924), TMPRSS2 (score =0.904) and CLEC4M (score =0.898). Function enrichment analysis against gene ontology in this network showed that for biological processes, this network is most enriched in cell division, small GTPase-mediated signal transduction and chromosome segregation.

Discussions

In our study, we analyzed the gene expression & immune infiltration profile with TCGA data followed by the assessment of ACE and ACE2 expression and co-relation level along with different pathological stages of lung cancer. We also demonstrated the clinical outcome of ACE & ACE2 with lung cancer and interaction network with these two enzymes and other proteins to know the depth of the disease and to consolidate known and predicted protein-protein association with ACE & ACE2.

Recent studies have revealed that, lung is one of the major organs where ACE & ACE2 are aberrantly expressed. In addition, a study found that lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) had much higher levels of ACE & ACE2 expression than did normal tissues. Intriguingly, however, another study using qRT-PCR and Western blot analysis revealed that overexpression of ACE2 suppressed ACE and angiotensin II type 1 receptor (AT1R) expression in human lung cancer xenografts while inhibiting cell proliferation and VEGFa production. These findings indicate a potential role for ACE2 overexpression in preventing NSCLC invasion and angiogenesis.

However, the expression and function of ACE2 in non-small cell lung cancer (NSCLC) are still unclear. But from the previous study, all together it is suggested that, ACE2 expression levels are upregulated during severe COVID-19 pulmonary disease.

Understanding these pathways would benefit from a comparison of lung tissue from SARS-CoV-2 infected patients with asymptomatic, mild, and severe COVID-19 disease. Unfortunately, it is yet unknown whether ACE2 overexpression is a direct cause of illness severity, a compensating protective mechanism, or merely an incidental phenomenon unrelated to disease severity. Given that a recent study found uniformly increased ACE2 expression in all severely affected COVID-19 lungs and negligible ACE2 expression in non-COVID-19 lungs, regardless of gender, it is unlikely that baseline pulmonary ACE2 expression levels influence the likelihood that COVID-19 pulmonary disease will develop in infected patients. According to a different study, lung cancer patients had a greater chance of overall survival when their mRNAs for ACE and ACE2 were expressed at high levels. A favourable initial advancement of lung cancer patients was connected with higher mRNA expression of ACE and ACE2. Patients with lung cancer who had upregulated ACE2 had good post-progression survival. Only ACE2 had the capacity to independently alter patients' prognoses for lung cancer in an independent prognostic study for ACEs.

In our work, by using several bioinformatics tools; expression of ACE was identified as a potential marker for the pathogenesis of lung cancer risk and after proper analyzing we found that ACE gene expression were statistically significant. Whereas, we have seen ACE2 expression were not significantly expressed both in lung Adeno Carcinoma (LUAD) and lung squamous cell carcinoma (LUSC) risks in TCGA datasets. Analysis using GEPIA2 online tool revealed the significant expression of ACE gene with LUAD & LUSC progression whereas ACE2 gene expression was not significantly expressed with LUAD & LUSC progression in TCGA datasets but Spearman's correlation found these both gene expression is positively correlated. The interesting fact about this is, in COVID-19 infected cases, the ACE2 gene is up-regulated, where in both LUAD and LUSC cases. There has been a correlation between smoking and the upregulation of ACE2 in LUAD and LUSC patients. It puts those patients at high risk of SARS-CoV-2 infection and possibly deadly outcome Prognostic value analysis by Kaplan-Meier Plotter revealed that, low expression of ACE mRNA decrease significantly overall survival probability & fast progression than high expression group for all lung cancer patients. At the same time, higher ACE2 expression causes shorter overall survival (OS) probability whereas, low expression causes shorter fast progression (FP) for all lung cancer patient and it was statistically insignificant. Although another web based bioinformatic tool analysis found its expression is significantly co-related with overall survival but in case of its expression with immune infiltration; CD8+ T cell, macrophages M1 and macrophages M2 were negatively correlated with LUAD patient's, however, mast cell activated was positively correlated with LUAD patient's. It is also positively correlated with mast cell

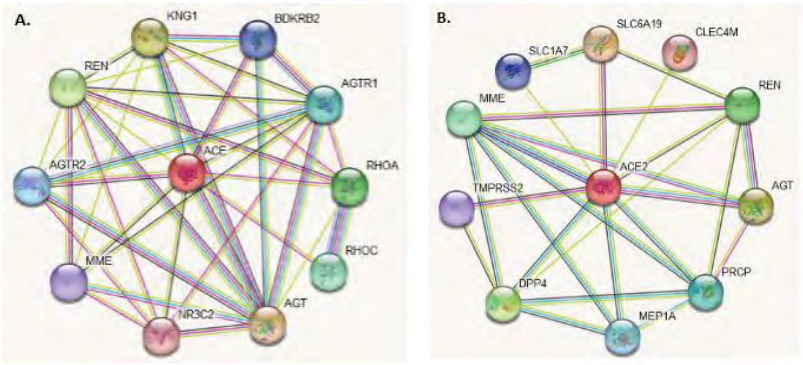

Figure 7: The interaction network of CCL18 and EGF protein with other proteins**.**

The interaction network was gained from STRING database for CCL18 **(A)** and EGF **(B)**.

Abbreviations: CCL18, C-C Motif Chemokine Ligand 18; EGF, Epidermal Growth Factor; STRING, Search Tool for the Retrieval of Interacting Genes.

activated, eosinophil and macrophages M1 and negatively correlated with T cell regulatory in LUSC patients. And the result was statistically significant. So, ACE2 expression has controversial role in predicting prognosis in these two common lung cancer types. STRING database were going through to find out the association of known and predicted proteins with ACE & ACE2. From the analysis it was seen that, only with ACE, there are 10 others genes are involve with different binding capacity whereas it shows 99.8% with AGT gene. The AGT gene has particular function of providing instructions for making a protein called angiotensinogen. Due to their strong binding, ACE will get more raw materials to make the situation more worsen which further creates different physiological problem such as constricts the blood vessels, increases blood pressure along with lung cancer severity. REN protein is part of the renin-angiotensin system, RHOA & RHOC originally studied in cancer cells where it was found to stimulate cell cycle progression and migration. Due to having strong binding capacity of ACE with them, it is speculated that, in case of LUAD & LUSC, cell differentiation will be greater. In case of ACE2, 10 other genes are also involved where particularly due to the association with AGT gene (99.8%) & REN protein (96.6%), it is confirmed that ACE2 will be over-expressed which role in lung cancer is controversial but severity of Covid-19 infection is clear as because it will allow the more entry site for the limitless access of SARS-CoV-2.

To summarize, our study that aberrant expression of ACE in lung cancer is greater than ACE2 and might be involved in the pathogenesis of lung cancer risk whereas ACE2 in Covid-19.

Conclusion

Our results indicate that, aberrant expression of ACE in lung cancer is greater than ACE2 and might be involved in the pathogenesis of lung cancer risk whereas ACE2 in Covid-19.

Ethics approval and consent to participate: Not Applicable

Consent for Publication: All authors agreed for publication

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

Competing interests

The authors have no conflicts of interest.

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Author Contributions

Sm Faysal Bellah: Conceptualization, Methodology, Formal analysis, Writing- original draft, Supervision. **Md. Robiul Islam**: Methodology, Writing - review & editing. All authors reviewed the manuscript. **Md. Tamimul Islam Tamim:** Analysis, Writing - review & editing. All authors reviewed the manuscript**, Mehedi Hasan Mamun:** Analysis, Writing - review & editing. All authors reviewed the manuscript.

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