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In silico prediction of COVID-19 cytokine storm in lung cancer types

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ABSTRACT

Lung cancer is one of the most frequently diagnosed malignant tumors and the leading cause of cancer-related death worldwide. Mainly, Non-small-cell lung cancer (NSCLC), which accounts for more than eighty-five percent of all lung cancers, consists of two major subtypes: lung adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC). Novel coronavirus disease (COVID-19) affected millions of people caused by acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) around the globe. Lung cancer patients and COVID-19 present unique and unfortunate lethal combinations because the lungs are the primary target organ of SARS-CoV-2 infection. Clinical studies have demonstrated that an over-activated inflammatory response associated with severe COVID-19 cases is characterized by excessive auto-amplifying cytokine release, which is defined as a "cytokine storm." ACE2 and TMPRSS2 receptors play an essential role in SARS-CoV-2 infection; therefore, using in silico analysis, we did correlation analysis with immune infiltration markers in LUAD and LUSC patient groups. Our study identified a promising correlation between immune-modulators and receptor proteins (ACE-2 and TMPRSS2), creating a domain that requires further laboratory studies for clinical authentication.

1. Introduction

In December 2019, a cluster of pneumonia cases was reported in people exposed to a seafood market in Wuhan, China. The medical investigation led to the emergence of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which subsequently rapidly spread all over the world; therefore, this disease was declared as a pandemic disease by World Health Organization (WHO) in March 2020 [1]. This pandemic's critical and devastating feature is not only limited to the discovery of new viruses but also diversifying and hyperinflammatory unpredictable immune response. According to current literature actual killer is not the virus but the immunologic complications such as hyper-proinflammatory status called the "cytokine storm" [2], leading to the development of acute respiratory distress syndrome and multiple organ dysfunction/failure, making the disease more grievous for COVID-19 patients [3,4].

Two receptors, i.e., angiotensin-converting enzyme 2 (ACE2) and the transmembrane serine protease 2 (TMPRSS2) are the crucial players in SARS-CoV-2 entry into host cells, thereby providing a platform to replicate and damage host cells and organs [3,4]. ACE2 acted as a functional "receptor" by facilitating the entry of the virus through the binding of spike glycoprotein (S-glycoprotein) of novel coronavirus SARS-CoV-2. On the other hand, TMPRSS2, the serine protease for virus spike (S) protein priming, facilitates the fusion of the viral and cellular membrane leading to viral internalization in the pulmonary epithelium protease indispensable for cell entry by SARS-CoV-2 virus [5]. Thus, cell membrane ACE2 and TMPRSS2 are proven key molecules for viral transmission and spread; understanding the underlying COVID-19 pathobiology could be decisive for the clinical outcome [5,6].

Despite technology fostering therapeutic innovation, lung cancer remains one of the most aggressive cancers and the leading cause of cancer-related death worldwide [7]. Lung cancers are broadly classified into two subtypes: small cell lung cancer (SCLC) and non-SCLC (NSCLC), which account for 15% and 85% of all lung cancers, respectively. NSCLC is the principal subtype which is predominantly divided into adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC) [8]. Huge variability among LUAD and LUSC is always a critical research point, therefore adopting different therapeutic strategies [8,9]. While all cancer patients remain vulnerable populations for COVID-19 infection, lung cancer patients get special attention due to the preexisting elevated

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levels of ACE2 receptor, thereby enhancing the entry and localization of SARS-CoV-2 and cytokines [10]. This unpredictability amplifies the importance of maintaining an urgent focus on the need to identify those patients who are at higher risk for COVID-19, thereby reducing mortality. Still, there are no reported characteristics of COVID-19-infected lung cancer patients [11], and targeted strategies to protect lung cancer patients (having low immunity) have not been identified yet [11]. Therefore, defining the features in different subtypes of lung cancer may become a vital cancer care strategy during this pandemic.

During this pandemic, the widespread term "cytokine storm" (CS) has captured the attention of the scientific community as well as the media, which can be described as "death signal" leading to the helplessness of health workers. The general concept of cytokine storm is the aberrant release of pro-inflammatory cytokines which is very well known; however an actual reason which can define the origin of cytokine storm is still lacking. "CS" constitutes of various cytokines (protein size smaller than 40 kDa; released with the aim of cell signaling), which encompasses various groups of interleukins, chemokines, interferon, tumor necrosis factor and growth factor [12–14]. Once the SARS-CoV-2 gain access of pulmonary epithelial cells, its internalization reduces the number of ACE2 receptors on a lung epithelium leading to an increase of angiotensin II in the blood [15,16]. Angiotensin II ignites an inflammatory cascade as part of the defense mechanism of innate immunity (Nonspecific) to combat and neutralize the virus [17]. However, ultimately, it triggers an inflammatory pathway which eventually results in excessive immune activation causing organ damage (severe pulmonary damage) instead of destroying the virus and restoring homeostasis [16,18–20]. Mitigating with cytokine storm offers a promising approach to treating COVID-19 patients, which can be further corroborated involvement of dexamethasone (anti-inflammatory) and Tocilizumab (IL-6R inhibitor) in clinics which showed promising therapeutic benefit in case of severe COVID-19 cases [21–23].

ACE2 and TMPRSS2 are the main interaction points of lung epithelium and SARS-CoV-2, making these attractive target ACE2 receptors one of the essential and attractive targets that utterly change the COVID-19 patients' prognosis [6,15]. However, there is enormous uncertainty about which patients' respond to therapy. Predicting the relevance of ACE2 and TMPRSS2 on the immune response mechanism, which could be determined in inviting cytokine storm, is vital to solving SARS-CoV-2 severity.

In this study, we probed the association of ACE2 and TMPRSS2 expression by GEPIA database with tumor immune cell infiltrating levels in LUAD and LUSC datasets available on TIMER and TISIDB web tool [10,24,25,27]. We identified a link between ACE2 and TMPRSS2 gene expression and various cytokines markers, which vary among lung cancer types. Our study sheds new light on the significant role of ACE2 and TMPRSS2 in lung cancers. It provides a new direction for further research for a comprehensive perspective of the pathogenesis mechanisms associated with SARS-CoV-2 infection in inviting cytokine storms in lung cancer patients [26].

2. Methods

Tumor Immune Estimation Resources (TIMER) analysis: We investigated the expression level in different tumor types compared to its normal tissue using TIMER web tool (https://cistrome.shinyapps.io/timer/) which gives analytical view on the RNA-seq data of malignant tumor in TCGA database. The statistical significance computed by differential analysis (edgeR) on RNA-Seq raw counts is annotated by the number of stars (*: P-value < 0.05). We also used this database to gain mechanistic insight in ACE2 mediated immunomodulation of various cytokine marker which primarily involve in "cytokine storm". TIMER database is a comprehensive resource for the systematic analysis of immune cell infiltrates in the microenvironment of various cancer types as reported earlier in breast cancer subtypes. It applies the deconvolution method to infers the abundance of tumor infiltrating immune cells from gene expression profiles [24].

Tumor-immune system interactions and drug bank database (TISIDB) analysis: It is an integrated integrated multiple public databases (http://cis.hku.hk/TISIDB/) including TCGA [39], was used to assess the correlation between ACE2 and TMPRSS2 and the tumor immune inflitreates (TILs) using a standard processing pipeline [25].

Gene Expression Profiling Interactive Analysis (GEPIA) dataset analysis: The online webserver, Gene Expression Profiling Interactive Analysis (GEPIA 2.0) (http://gepia2.cancer-pku.cn/) is online website tool to analyze the RNA sequencing expression data clinical samples of tumors and normal patients samples in The Cancer Genome Atlas (TCGA) and Genotype Tissue Expression (GTEx) dataset projects [37]. It was used to find the expression differences of ACE2 and TMPRSS2 between the LUAD, LUSC and corresponding normal lung samples using a standard processing pipeline. The threshold were set as following: *P*-value of 0.05, fold change of 0.5, matched TCGA normal and GTEx data [27].

MetaboAnalyst: The data were analyzed using the statistical package in MetaboAnalyst 4.0 [http://www.metaboanalyst.ca/MetaboAnalyst/] for generating heat maps. TIMER dataanalysis were utilized logarithmic transformation and a column wise normalization applying MetaboAnalyst 4.0. The statistical significance is annotated by the number of stars (*: *P*-value < 0.05; **: *P*-value <0.01; ***: *P*-value <0.001; ****: *P*-value <0.0001) [28].

3. Results

The mRNA expression level of ACE2 and TMPRSS2 between Lung Cancer and normal lung tissues was analyzed by the GEPIA database [27]. GEPIA results (Fig. 1) indicated that ACE2 expression was significantly upregulated in LUAD (Fig. 1A) and TMPRSS2 expression level was significantly downregulated in LUSC (Fig. 1D). However, there were no differences in mRNA expression levels of ACE2 in LUSC and TMPRSS2 in LUAD between tumor and normal tissues in lung cancer patients (Fig 1A; 1D). In order to understand *m*-RNA expression level variation at different tumor stage we analyzed the GEPIA database. Obtained result suggested that except for TMPRSS2 expression in LUSC (Fig. 1E), none of the analyses varied in the different tumor stages (Fig. 1B, C & 1F). The expression of TMPRSS2 with tumor stage for LUSC was positively and highly associated ($P < 0.05$) with advanced cancer stages (Fig. 1E).

In order to explore the corealtion between ACE2 or TMPRSS2 and cancer immunity, we utilized the Tumor and Immune System Interaction Database (TISIDB, http://cis.hku.hk/TISIDB) to analyze the potential relevance of these genes in regulating tumour infiltrating lymphocytes (TILs) across 30 cancer types [25]. The outcomes of analyses (Fig. 2) showed that ACE2 (Fig. 2A) and TMPRSS2 (Fig. 2B) expression levels correlated positively or negatively with the relative abundance of almost all types of TILs with tumor-suppressing or tumor-promoting functions across 30 types of cancers.

Furthermore, to understand the significance of this higher expression, we analyzed the correlation coefficient between the ACE2 and various cytokines markers which constitute CS, i.e. chemokines, interleukins, tumor growth factor (TGFβ1, TGFβ2, TGFβ3), interferon (IFNα1, IFNβ1, IFNγ) and colony-stimulating factor in both LUAD and LUSC. A heat map was generated to summarize the results in Fig. 3 [12]. In detail, we have explored the correlation coefficients of ACE2 and TMPRSS2 expression with 29 cytokines in LUAD and LUSC (Supplementary Table 1). Obtained data suggested that in LUAD, correlation coefficients of ACE2 were negatively and significantly associated with the infiltration of 18 cytokines. On the contrary, only 4 out of the total 29 cytokines were significantly negatively correlated in LUSC, implying a robust inhibitory role of ACE2 in preventing cytokines in LUAD compared to LUSC.

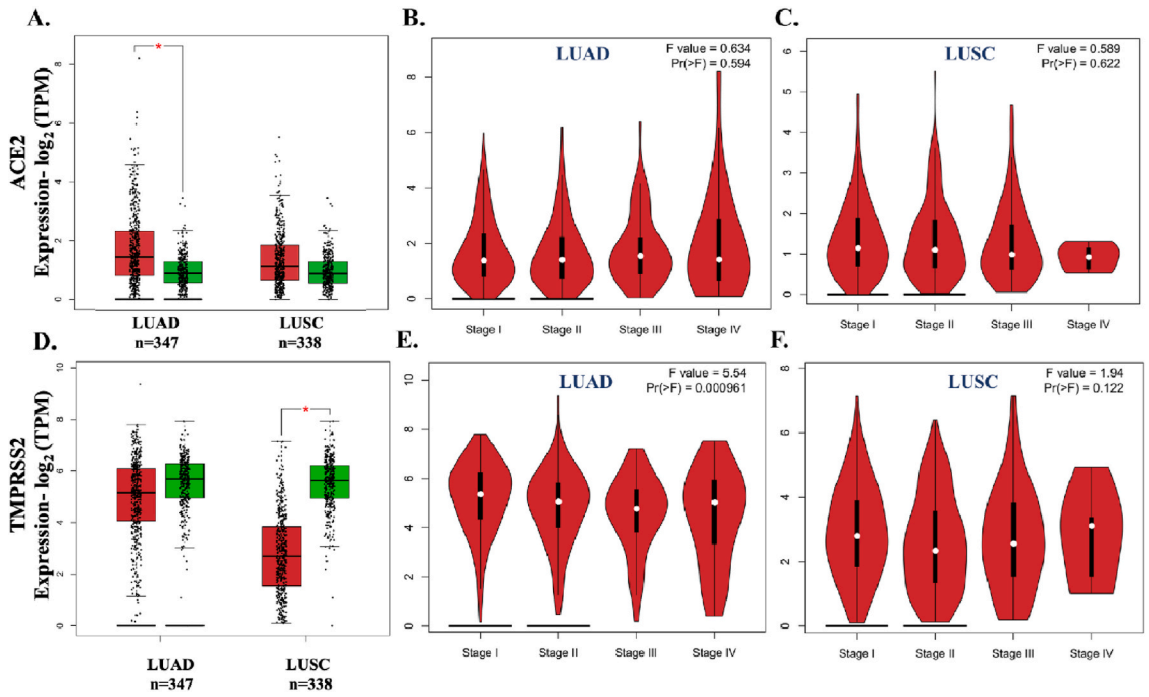

Fig. 1. The distribution of ACE2 and TMPRSS2 mRNA expression trends in lung tissues: (A) the distribution of ACE2 mRNA expression in LUAD and LUSC between tumor tissue represented in red and normal tissues represented in green; **(B)** correlation between ACE2 expression level trends in different LUAD pathological stages; **(C)** correlation between ACE2 expression level trends in different LUSC pathological stages; **(D)** the distribution of TMPRSS2 mRNA expression in LUAD and LUSC between tumor tissue represented in red and normal tissues represented in green; **(E)** Correlation between TMPRSS2 expression level trends in different LUAD pathological stages; **(F)** Correlation between TMPRSSS22 expression level trends in different LUSC pathological stages Abbreviations: LUSC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma; GEPIA, gene expression profiling interactive analysis; T, tumor; N, normal control. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

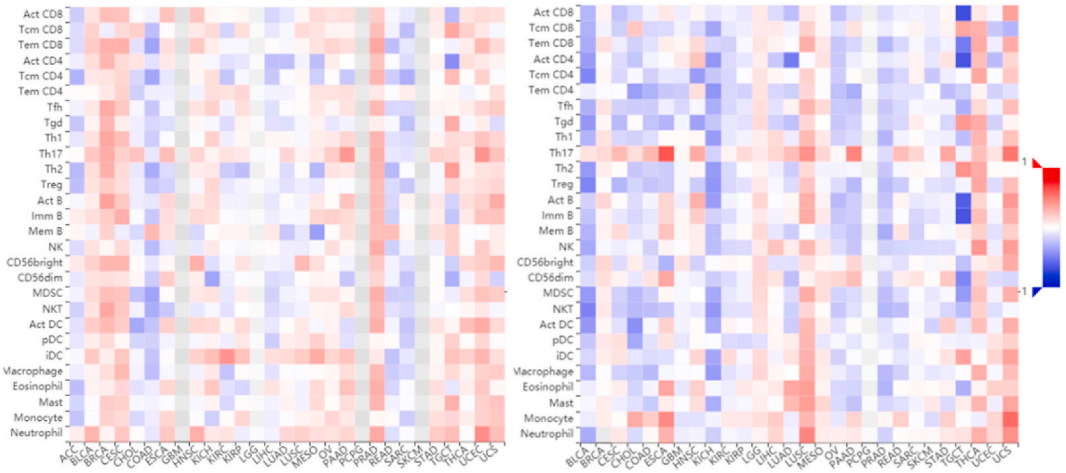

Fig. 2. Correlation between ACE2 and TMPRSS2 expression and lymphocytes. The pan-cancer analysis of relationship between abundance of the 28 tumor-infiltrating lymphocytes (TILs) and (A) ACE2 and (B) TMPRSS2 expression.

4. Discussion

A weakened immune system (immunocompromised) makes cancer patients vulnerable to increased risk for severe illness from COVID-19. ACE2 and TMPRSS2 expressions show higher and lower expression in both groups than in normal lung tissue [12]. Sagkan et al. found no significant difference in the LUAD group between normal and tumor tissue, contradicting our report. This is due to a change in parameter from 1 to 0.5, which led to a significant difference. Various preclinical models have been demonstrated the protective effect of ACE2 [12] and also involved in cytokine storm-driven inflammation [29]. Due to ACE2 and TMPRSS2 gene overexpression in lung cancer it became critical to understand cytokines infiltration in lung cancer subtypes [30]. Surprisingly, some of the clinically proven essential cytokines in the case of COVID-19, such as IL-6, which served as a biomarker for COVID-19 infection [31,32] was negatively correlated in LUAD ($P < 0.0001$) compared to LUSC with ACE2 gene expression, where it has shown a non-significant correlation. Various other essential cytokines which constitute "cytokine storm" such as IL-2R, TGFβ1, TGFβ2, IFNα1, IFNβ1, IFNγ, CXCL10 and MCP2 [4,17,33] were also negatively correlated in LUAD (Fig. 3 and Supplementary Table 1). Interestingly this pattern was followed when we correlated with TMPRSS2 gene expression

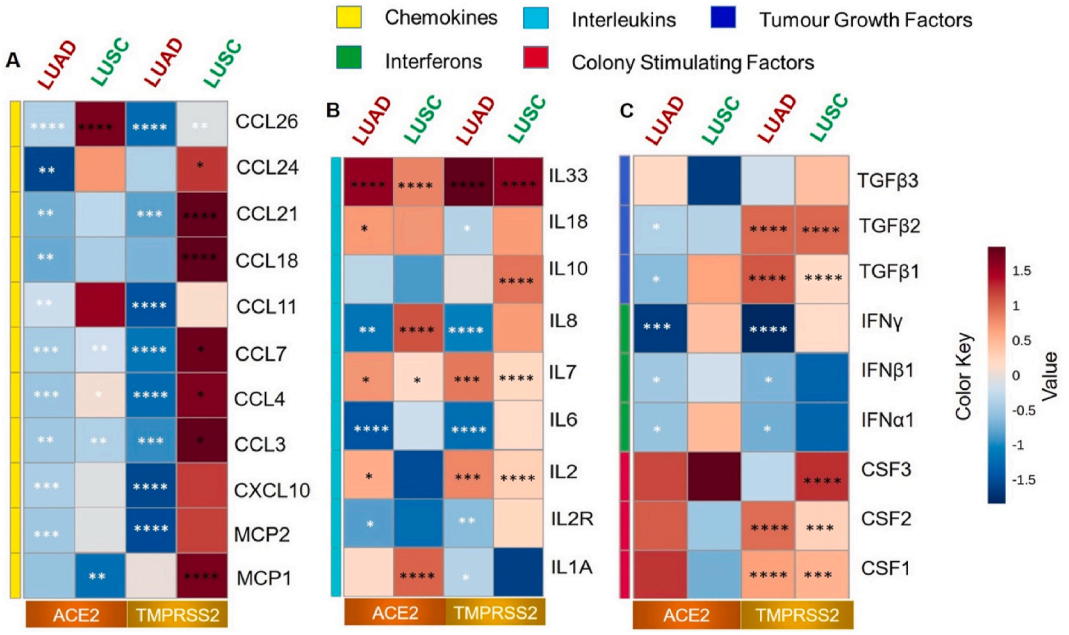

Fig. 3. Correlation analysis between ACE2 and TMPRSS2 with immune infiltration level. Heatmap clustering analysis performed in MetaboAnalyst 4.0 showed the spearman correlation-based analysis with the level of significance of immune-modulators with ACE2 and TMPRSS2 expression in LUAD and LUSC using TIMER analysis. MetaboAnalyst 4.0 was used for generating the Heat map (https://www.metaboanalyst.ca/MetaboAnalyst/ModuleView.xhtml). Colored bars represent differential levels of Spearman's correlation. Blue represents negative correlation values while the red represents the positive correlation values. TIMER web tool (https://cistrome.shinyapps.io/timer/) was used for statistically analyzing the correlation values. The statistical significance is annotated by the number of stars (*: *P*-value < 0.05; **: *P*-value <0.01; ***: *P*-value <0.001; ****: *P*-value <0.0001). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

accounting for total 16 cytokines that were negatively correlated in LUAD. On the contrary, in LUSC, only CCL26 was significantly negative, confirming the close involvement of ACE2 and TMPRSS2 among lung cancer subtypes and in immunomodulation.

Due to the increasing importance of immune imbalance in the pathogenesis of SARS-CoV-2, various immune-modulating drugs seem to be determinants in treating COVID-19 patients [34–36]. Similarly, the trend of our data also indicates that ACE2 expression had a negative correlation coefficient with most of the cytokines in LUAD, indicating ACE2 preventive role in cytokine stimulation. Collectively, we can

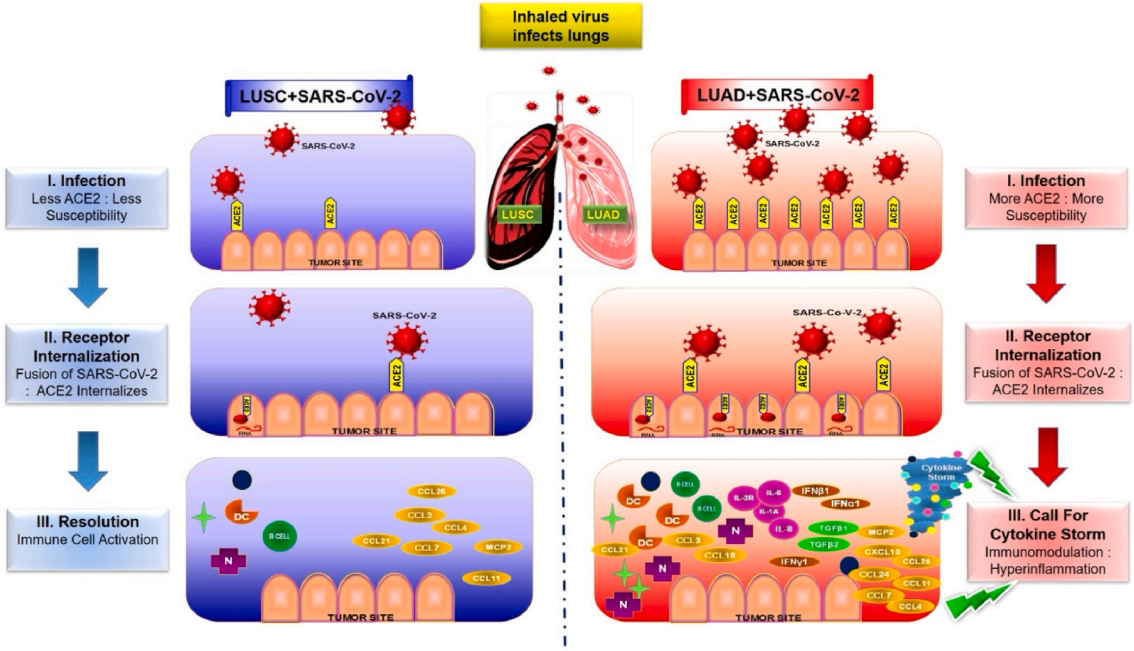

Fig. 4. - Three steps predictive model of SARS-CoV-2 consortium with lung cancer types: The predictive implications towards the ACE2 inhibitors in lung cancer types has been shown in three major steps i) *Infection*: As high expression of ACE2 in LUAD leads to increase in virus susceptibility compared to LUSC. ii) *Receptor internalization*: A major step in immunomodulation and provoking cytokine storm due to negative correlation of ACE2 with immune modulators in LUAD. iii) *Call for cytokine storm/Resolution*: Hyper-inflammatory response in LUAD while it diminishes the immune response in LUSC.

interpret from TIMER database analysis a significant negative correlation of major cytokines implying that ACE inhibitors in these patients will decrease the probability of inviting cytokine storm, therefore, avoiding the COVID-19 severity [22,24]. On the contrary, LUSC ACE-2 is positively correlated with various cytokines, suggesting that in LUSC patients, SARS-CoV-2 infection may not call for cytokine storm, providing (Fig. 4) a better therapeutic window that includes other options such as plasma therapy; however, further studies are warranted to corroborate these finding. The various therapeutic approaches hinder the ACE2 interaction with the SARS-CoV-2 virus by blocking its entry [37,38]. As ACE2 interaction with virus spike protein is essential to establish the infection, we can predict that hindering the interaction using small molecules or ACE receptor blockers can be a better therapeutic approach in LUAD however, further clinical validation required to prove this finding [23,39].

Based on our results, we suggest that ACE receptor blockers can be recommended in the case of LUAD to prevent “cytokine storm” as these patients are more vulnerable to infections and cytokine storm. On the contrary use of ACE2 and its ligand or COVID-19 virus spike protein, recombinant human ACE2 protein (rhuACE2) [26,40] may provide a better alternative to therapeutic relief in LUAD patients. However, it is very preliminary in silico based study; experimental validation of these findings in clinics will not only forecast but also provide a speedy computer base prediction for the immunomodulatory approach, giving cancer researchers a “head start” in tackling the COVID-19 outbreak.

5. Conclusion

Our study predicted a correlation between immune-modulators and virus receptor proteins using a computational approach and shed light on immunomodulatory therapies to overpower the deregulated pro-inflammatory action in COVID-19. Overall, our study elucidated differential vulnerability and complications toward SARS-CoV-2 infection in lung cancer types, necessitating a comprehensive and multidisciplinary treatment approach for a better outcome during the current pandemic. On one hand in terms of operational factors and therapeutic outcomes, computational models and simulations offer significant advantages over human-based clinical trials howver bioinformatics studies has also some limitations associated with it. As our study is based on publicaly available tools and datasets, so outcome of this study further warneted immune analysis using FACS and other surface marker protein in lung cancer will help in better understanding the role of immune playres in subtypes. where we have used only the publicly available tools and datasets in this analysis.

Author contributions statement

The authors contributed in the following way: design and write the manuscripts: R.M and S.S, T.P.C, PKY, DK, SK, AS; provide materials: S. S; perform analysis: GS, SA; interpret data: S.S, and R.M.

Declaration of competing interest

No potential conflicts of interest were disclosed.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bbrep.2022.101350.

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