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COVID-19 patients' sera induce epithelial mesenchymal transition in cancer cells

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ABSTRACT

Covid-19 Pneumonia of SARS-CoV-2 pandemic infection, persists to have high disease burden especially in cancer patients. Increased inflammation and thromboembolic processes are blamed to influence cancer patients more than the others but due to lack of knowledge regarding the pathophysiology of the both the virus itself and the response of the host, more basic and translational disease modeling research is needed to understand Cancer-Covid-19 interaction. In this study, serum samples from the patients, who were hospitalized due to Covid-19 pneumonia, applied to different cancer cells and cytotoxicity, motility, proliferation and gene expression analysis were performed. Serum samples derived from healthy volunteers and the fetal bovine serum that is used regularly in cell culture experiments used as controls. Hospitalized Covid-19 patients who had also cancer, were retrospectively screened, and their clinical course were recorded. Overall 12 Patient (PS) and 4 healthy serums (CS) were included in the experiments. PS applied cells showed increased motility in A549 cells as well as lost cell to cell connection in MCF7 and HCT116 cells, and induced expression of *VIM, ZEB1* and *SNAIL2* mRNA levels. Eight cancer diagnosed patients who were hospitalized due to Covid-19 between April and September 2020 were also reviewed retrospectively, which 5 of them were dead during SARS-CoV-2 infection. Thorax CT images of the 2 patients showed increased metastatic nodules in the lungs as of January 2021. The results of the study indicate that metastasis may be one of the prolonged consequences of COVID-19 pandemic in cancer sufferers.

List of Abbreviations

CP:	Cancer patients
CS:	Control (healthy) serum
CT:	Computed tomography
EMT:	Epithelial to mesenchymal transition
FBS:	Fetal bovine serum
MTT:	3-(4,5-dimethylthiazol-2-yl)−2,5-diphenyltetrazolium bromide
PS:	Patient serum
RPMI 1640:	Roswell Park Memorial Institute, Medium

Introduction

The COVID-19 disease caused by the SARS-CoV-2 infection, which emerged in Wuhan, China at the end of 2019 and affected the whole world throughout 2020, continues to be a multi-unknown disease by the beginning of the second year of the pandemic. As of January 2021, nearly 100 million cases and over 2 million deaths related to COVID-19 have been detected. Disruptions in the diagnosis and treatment process of many diseases, especially cancer due to the pandemic, and even the secondary morbidity and mortality burden are not included in these numbers. The disease progresses with different pictures ranging from

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asymptomatic carriage to respiratory failure, and the clinical course is relatively severe in patients with comorbidities [1]. Among them, cancer deserves attention that we still have very little information on how these infection effect tumor cells, is the response to the infection changes between the different type of cancers or is there any way to change the arrows backwards to the virus during infection. There are studies that show patient with cancer had more severe Covid-19 symptoms or deaths comparing to non-cancer Covid-19 patients [2,3], and proposed theories that might lead the pathophysiology during the process [1,4]. The increased micro-thrombo-inflammatory syndrome is one of the suggested theories that gives rise to the failures of multiple organs and thus, to the deaths [1]. The other potential pathways in Covid-19 to induce cancer progression include inflammatory-related pathways that directly affect tumor microenvironment via activating angiotensin- 2 system which takes place in neovascularization of tumor cells, heat shock protein 27-cytokine activation system that has impact in cancer cell signaling, epithelial to mesenchymal transition (EMT) system which drives cells to metastasis [4], products released from activated neutrophils known as Neutrophil extracellular traps (NETs), which contain DNA and web-like structures of proteins that leads dormant cancer cells to escape from the immune-active area [5]. A recent study claimed that SARS-CoV-2 increased ZEB1 expression, to promote EMT in lung cancer cells [6], and there are also previous works that introduced proofs for acute and chronic inflammation to have ability to induce EMT in in-vitro and in-vivo studies [7]. Weather the virus itself triggers the mechanism or the inflammatory mediators, there is still more is urged to understand the biomolecular background of the Covid-19 cancer interactions.

In this study, we hypothesized that the serum samples of Covid-19 patients, that must have contained various well-known cytokines such as IL-6, IL-1, TNF- in different amounts among each patient, and unknown mediators as microRNAs, circulating cell free DNAs (ccfDNA), or long non coding RNAs (lnRNAs), as well as viral peptides and other particles, that might orchestrate all together to have an impact on the proliferation and/or motility of cancer cells.

Materials and methods

Study design, participants and serum sample collection

The patients, who were hospitalized due to laboratory-confirmed diagnose of COVID-19 pneumonia and who gave written consent to be included in the study between March and December 2020 were included in the study. Demographic data including, age, gender, medications, comorbidities, duration of hospitalization, the need of critical care and laboratory results in the first day of admission were recorded. Serum samples were collected on the first 24 h of the admission of the patients which they all were on the first day of Favipiravir treatment and some of them had also received corticosteroids and oxygen supplementation due to their hypoxia. Collected serum samples were used immediately in the cell culture experiments or froze at −80 °C no more than 1 week if later use is decided. The records of hospitalized patients who also had cancer as comorbidity were retrospectively screened for their clinical course and prognosis after SARS-CoV-2 infection.

Cell lines, cell culture and reagents

Frequently studied carcinoma cell lines in EMT related research including human lung adenocarcinoma cell line A549, mammary carcinoma cell line MCF7, hepatocellular carcinoma cell line HUH7 and colorectal carcinoma cell line HCT116 used for proliferation, cell motility and gene expression analysis in-vitro experiments. Human BEAS2B bronchial epithelial cells and human primary fibroblast cells were also used for cytotoxicity assays. Cells were grown in RPMI 1640 media (HyClone) with 10% FBS (HyClone) supplementation and washed at least 2 times with 1X Phosphate Buffered Saline (PBS) solution (HyClone) before adding human or reduced serum samples.

Cytotoxicity and proliferation assays

10^3 cells per-well were seeded in 96 well plates and incubated for overnight in regular growth media. Next day, the old FBS containing media was removed, cells were washed with PBS and treated with increasing concentrations of patient or healthy (control) serum, diluted in serum free RPMI for 24 h. For cytotoxicity assay, at the end of 24 h, MTT (3-(4,5-dimethylthiazol-2-yl)−2,5-diphenyltetrazolium bromide) (BioFROXX), dissolved in PBS was added at 0.5 mg/mL concentration to each well and incubated for another 4 h. Then the media was carefully removed and 50μL of ethyl alcohol was added to each well to dissolve the cells. Absorbance was measured immediately at 570 nm in a microplate reader (Biochrom EZ read 400). For the proliferation assays, equal amount of patient and health volunteers' serum samples were incubated for 24, 48 and 72 h and MTT test was performed as described in cytotoxicity protocol at the given time points.

Cell motility assay

A549 cells were allowed growing at 100% confluency in 3 cm plates and starved overnight. Next day a scratch line was made using a 10 μl pipette tip in the center of the plate, rinsed with PBS and treated with indicated concentrations of FBS (as control) or patient serum diluted in serum free RPMI media. Images were obtained at time 0 and 24 h. Percent closure of the scratch area was measured using ImageJ (v 1.53, NIH, USA) software.

Quantitative polymerase chain reaction experiments (qPCR)

Cells were seeded to 10 cm plates in 10% FBS and after they reach 70% confluency, they were overnight starved (incubated with serum-free RPMI) before adding 3% patient serum or control serum. RNA was isolated after 4 h of incubation using RNA isolation kit (Thermo Scientific, #K0732) quantified fluorometrically using RNA quantification system (QuantiFlour, Promega), and reverse transcribed via cDNA synthesis kit (ABM, #G234). For qPCR experiments, primers were designed using 2 different primer design tools (IBT technologies P-Quest and NCBI-BLAST) and listed as follows: *SNAIL2* F: 5′- GCGATGCCCAGTCTAGAAA-3′ and R: 5′-GGTAATGTGTGGGTCCGAATA-3′; *ZEB1* F: 5′- CTTCTCACACTCTGGGTCTTATTC-3′ and R: 5′-CGTTCTTCCGCTTCTCTCTTAC-3′; *VIM* F: 5′- CAGCTTTCAAGTGCCTTTCTG-3′ and R: 5′- CTTGTAGGAGTGTCGGTTGTT-3′; *18S* F: 5′-CTTAGAGGGACAAGTGGCG-3′ and R: 5′-ACGCTGAGCCAGTCAGTGTA-3′ qPCR protocol was optimized according to 2X SYBR Green (Ampliqon RealQ Plus (2X) #A324402) protocol. 18S was used for internal control gene and 2^-(delta CT) calculations were performed to determine the fold differences between patient serum treated samples and controls.

Statistical analysis

Prism V8 software (GraphPad, USA) was used for calculations and the design of all graphics. Normalization, logarithmic transformation of the data and non-linear regression-curve fit analysis were used for IC_{50} determination. To compare the differences in serum or control treatments in scratch assays, non-parametric two-tailed Mann Whitney test was used, and significance was considered when $p<0.05$.

Ethical issues

Study was approved by Turkish Ministry of Health Scientific Board and Cukurova University Ethical Committee (2021/108–17). All the participants have given written consent to involve in the study.

Table 1
Characteristics of patients and controls.

Patient / Control Sera #	Age	Gender	Fever	Hypoxia	Hb (g/dL)	Platelet count (x10^3)	D-Dimer (mg/L)	Fibrinogen	Ferritin	CRP (mg/L)	Co-morbidity
PS#1	56	M	No	Yes	14,4	365	0,34	479	520	85	None
PS#2	45	M	No	No	13,4	142	0,43	377	123	10	None
PS#3	79	M	No	No	12,8	138	1	463	104	51	Malign Melanoma, HT
PS#4	77	M	Yes	No	11,6	95	0,53	550	486	116	DM, HT
PS#5	70	M	Yes	No	10,1	11	1,6	236	1637	10	AML
PS#6	76	F	No	Yes	11,2	134	0,37	398	1794	99	HT
PS#7	66	M	No	No	14,2	189	0,53	463	187	17	HT
PS#8	71	M	No	Yes	13,7	257	0,79	398	307	36	None
PS#9	35	F	No	No	13,9	206	0,34	387	16	5	None
PS#10	55	M	No	No	15,3	214	n/a	522	157	140	None
PS#11	66	M	No	Yes	14,9	374	n/a	522	1310	184	None
PS#12	53	M	No	Yes	13,7	181	0,4	421	342	49	Asthma
CS#1	43	M	No	No	-	-	-	-	-	-	None
CS#2	36	M	No	No	-	-	-	-	-	-	None
CS#3	46	F	No	No	-	-	-	-	-	-	None
CS#4	65	M	No	No	-	-	-	-	-	-	HT

PS: Patient Serum; CS: Control serum, M: male; F: female; DM: Diabetes Mellitus; HT: hypertension; AML: acute myeloid leukemia; HL: hyperlipidemia; n/a: not applicable.

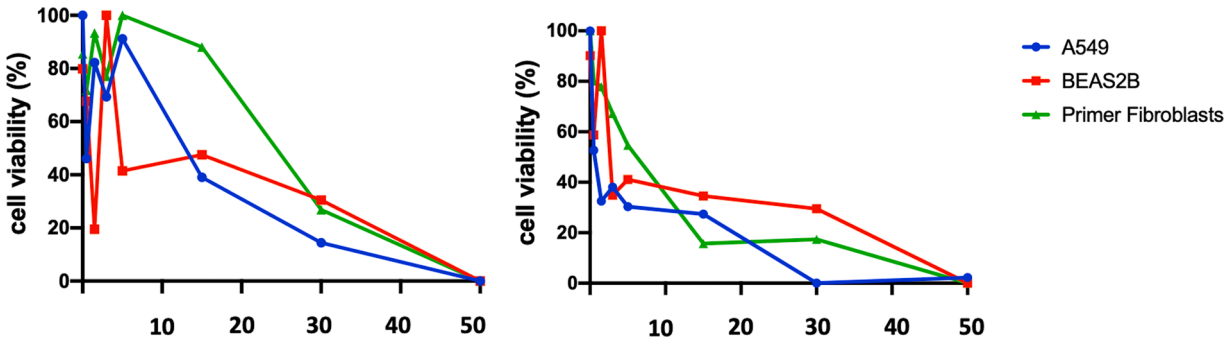

Fig. 1. Cytotoxicity of Covid-19 Serum samples. Serum obtained from two different Covid-19 patients (PS#2 #1 on the left and PS#2 on the right) was given to three different cell types in increasing concentrations (0 to 50% per volume) in FBS free RPMI-1640 media. MTT test was performed to stain live cells and absorbance was measured at 570 nm wavelength. Viability of the cells decreased in the increasing concentrations of serum application in 24 h.

Results

Demographic parameters of the patient and control group

Serum samples from 12 Covid-19 patients and 4 healthy volunteers were obtained for the in-vitro experiments. The list of patients and control subjects and their related parameters are given in Table-I. The mean age of the patients was 61,16 (12,71), and 83% (n = 10) were male, and the mean age of the control group was 42(12), and 75% (n = 3) were male, therefore, age and gender matched controls used to compare the results in each individual experiment.

Serum samples of COVID-19 patients were cytotoxic at high concentrations

We run cytotoxicity tests on bronchial epithelial cells, primary lung fibroblast cells and A549 lung adenocarcinoma cells using 2 different patient samples PS#1 and PS#2 to analyze cell killing activity of the derived serum samples. We have chosen these cell lines in order to evaluate cytotoxicity to cancer cells as well as non-cancerous cells and to decide a minimal study concentration for the experiments, since we would be able to collect small amounts of serum samples from each patients and controls. Concentrations applied to cells were 0%, 0.5%, 1,5%, 3%, 5%, 15%, 30% and 50% per volume, and no significant difference was observed in the results of PS#1 and PS#2, or between the different types of cells (Fig.-1). Viability of the cells were dropped to 50% in 24 h at around 15% concentration per volume for PS#1 and around 3% concentration for PS#2. Therefore, we decided to use 3% PS as a minimal amount of study concentration for the next experiments.

Serum samples of COVID-19 patients increased cell motility of cancer cells

The accumulating data indicate that SARS-CoV-2 induces the regulation of variety of genes to comfort its replication, and one of these genes is *ZEB1*, which plays an important role in the epithelial to mesenchymal transition (EMT) and has an impact on cell motility and metastasis of various cancers[5]. While the virus itself might trigger this process, the need for prolonged treatment with corticosteroids due to the persistent fibrotic pattern in these patients brings in mind that the stress related mediators, cytokines, cellular components that release from the shredded cells might have contribute to the scenario. Therefore, we designed a motility test using serum sample derived from patient #3 (PS#3), who were also diagnosed with stage IV malign melanoma at the

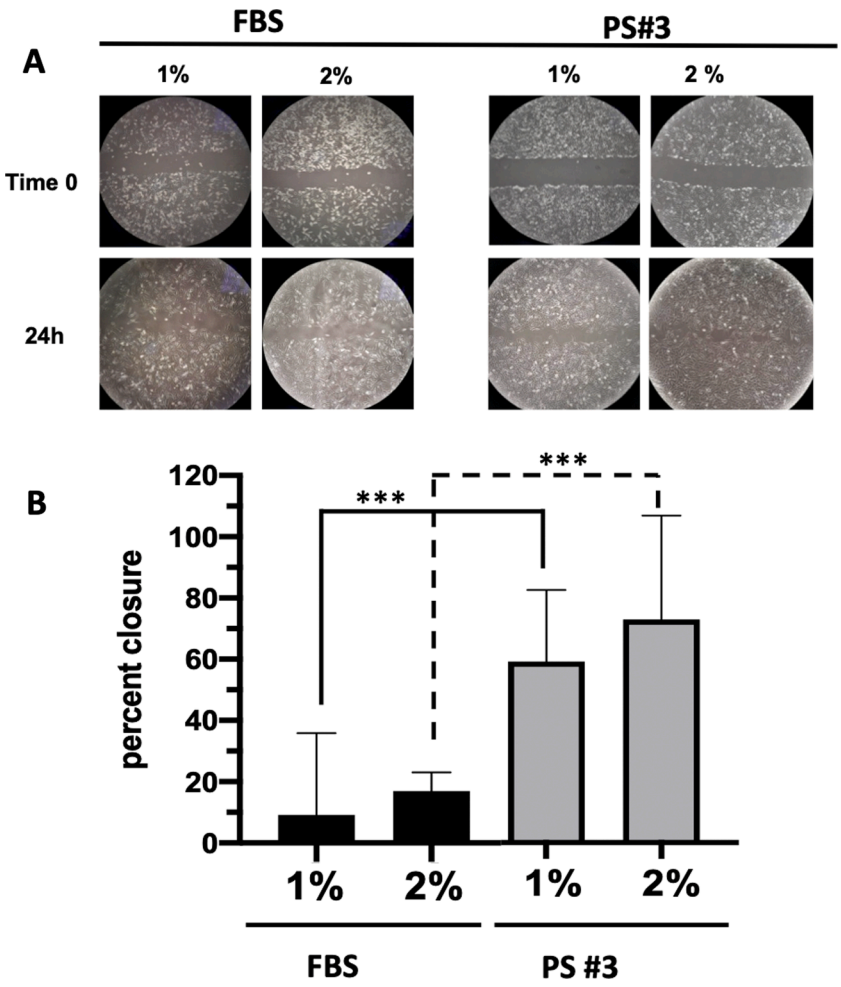

Fig. 2. Cell motility effect of Covid-19 patient serum on the cells. PS#3 was tested for motility assay on A549 cells and closure ratio differences between PS# and FBS were compared at 2 different concentrations. The cells were overnight serum starved before the generation of the scratch. Cell images were obtained at Time 0 and 24th hour of the treatment (A). Bar graph represents average percent closure measurements from 10 different areas from the images and 1 and 2% application of PS# treatments significantly increased the motility of A549 cells comparing to equal amount of FBS (*** $p<0.001$) (B).

time of Covid-19 diagnose. We compared the motility effect of PS#3 with fetal bovine serum (FBS) on A549 cells and the results revealed that 2% of PS#3 significantly increased closure ratio of A549 cells comparing to 2% FBS (Fig.-2). We also repeated this experiment using 2 more PS and CS and observed similar results, which we provided in the Supplementary Figure 1.

Serum samples of COVID-19 patients increased expression of EMT related genes

We obtained serum samples from patients and healthy volunteers and evaluated the difference between the expression of mRNA levels of EMT related genes *VIM* (Vimentin*), ZEB1* and *SNAIL* in different cancer cell lines. We used age and gender matched control serums for each experiment. Results of qPCR experiments indicated that most of the cells responded to Covid-19 patient serum by increasing the expression of at least one of the EMT related genes (Fig.-3). The baseline CT values are provided in Supplementary Table-1.

Prolonged PS treatment induced changes in the morphology of the cells while suppressing proliferation

We repeated the cytotoxicity tests with 3 more PS samples and no significant difference was observed in the viability of A549 cells (Fig.-4). Only one PS (PS#10) tended to increase proliferation at 20% concentration. We than run a series of proliferation tests to evaluate the prolonged effects of PS in A549, MCF7 and HCT116 cells comparing to FBS controls. The results revealed that in most of the cells, PS's suppressed cell proliferation at 24, 48 and 72 h (Fig.-4), which might be related with the half-life of the serum ingredients of the patient sera. On the 48th hour, we experienced that the cells de-attached from the plate very easily during MTT test and therefore we took images of the cells at this time-point and visualized the intercellular connection loose between the PS treated cells (Fig. 4). We also repeated this experiment by replacing the serum containing media in every 24 h in order to overcome the possible consequences related with the duration of the human serum samples. We used fresh serum on the time 0, and aliquoted and frozen serum at 24th hour and images were obtained at the 48th hour, which indicated similar results (Supplementary Figure 2).

Patients show increased pulmonary metastatic lesions 6 months after SARS-CoV-2 infection

We retrospectively screened Covid-19 patients' files that were hospitalized between April to September 2020 and who were also had diagnosed with cancer. After excluding hematologic malignancies, we recorded 8 patients whom 5 was already death by January 2021. The characteristics of the Covid-19 Cancer patients (CP) are listed in Table-II. For the rest 3 patients, all diagnosed with Covid-19 in August 2020, we had 6th-month computed tomography (CT) images for two of them with increased pulmonary metastatic nodules (Fig.-5), which one of them is the same patient that serum samples were used in Figure-2. We

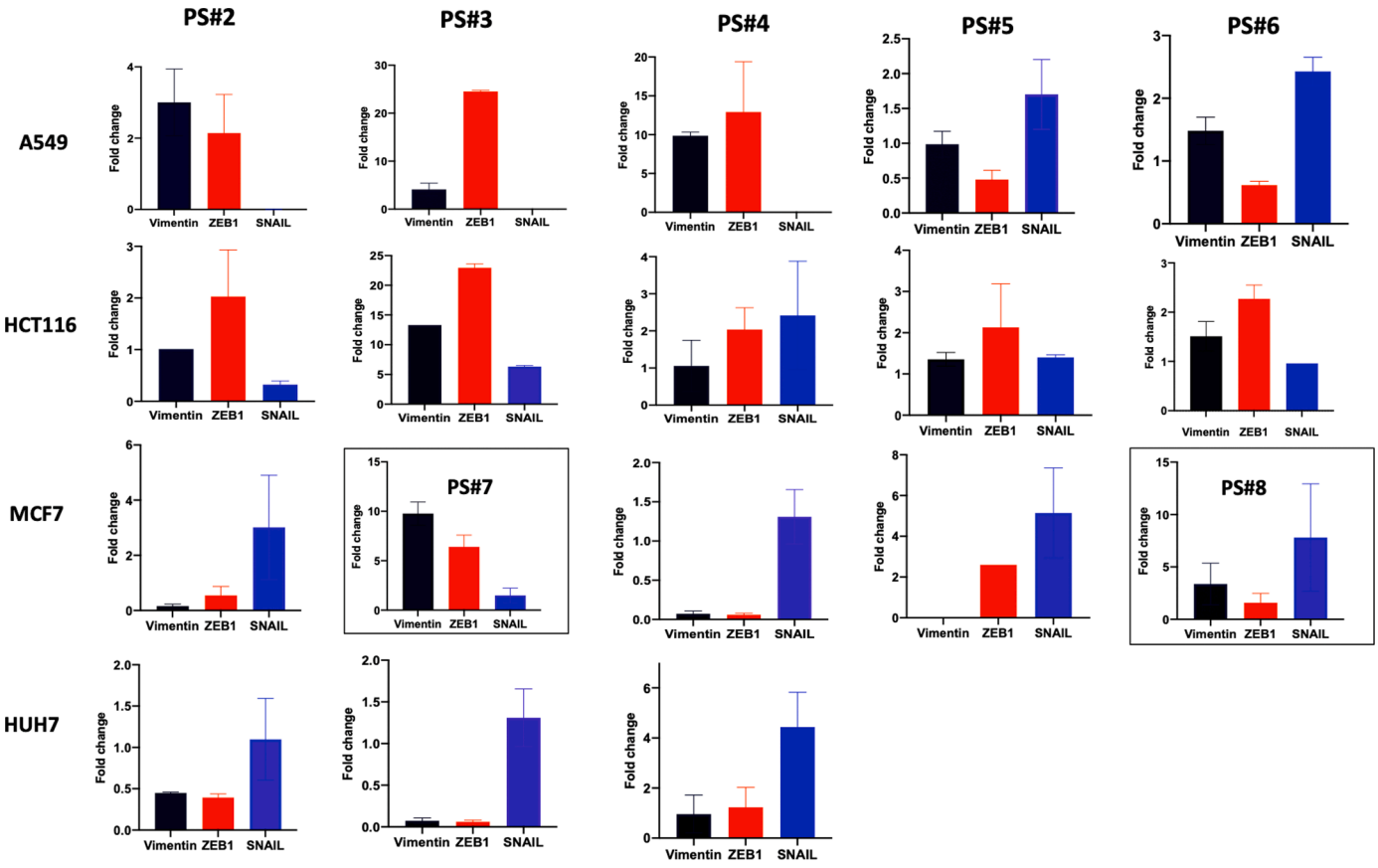

Fig. 3. Effects of serum on the expression of EMT genes *Vimentin, ZEB1* and *SNAIL2*. Four different cancer cell lines were incubated with equal amounts of age and gender matched patient serum (PS) and Non-Covid healthy control serum (CS) for 4 h and the differences in the expression of the genes were evaluated via qPCR. Fold change between PS and CS was calculated using comparative CT method. The results indicate that most of the PS led to an increase in the mRNA expression levels of at least one of the EMT related genes. For comparisons, CS#1 was used for male PSs (2,3,4,5,7 and 8) and CS#3 was used for female PS (PS#6).

could not obtain control CT images of the last CP.

Discussion & conclusion

In this research, we designed a series of in-vitro experiments to contribute understanding of how Covid-19 might influence various cancer cells during its course and we have shown that serum samples of Covid-19 patients increase cell motility, induce expression of EMT related genes in four different cancer cell lines and lead to morphological changes in these cells. The findings of this study are significant due to the testing the complete serum of the patients instead of individual inflammatory molecules or virus, which untested elements would be ignored and might cause bias in the results. Since we had limited amounts of serum samples from each patient, we could not run all of the experiments as well as could not repeat individual experiments with the same patient's sera. The prolonged effect of the sera on EMT related gene expression is not evaluated in this research which can be counted as another restriction. The blood parameters regarding the inflammation or the clinical courses of the patients, whose sera were used, were not similar in this study suggesting that the cancer patients might become vulnerable to disease progression after having Covid-19 regardless of the severity of the infection. Still, it is hard to generalize these findings to the whole cancer types that every one of them should be considered as different diseases.

In this study, we also provided CT images of 2 patients who had advanced stage cancer and infected with SARS-CoV-2 in August 2020 and had increased pulmonary metastasis in early January 2021. Obviously, it is hard to conclude that Covid-19 infection is purely responsible from these increased metastases, but it indicates the need to evaluate a cohort group of cancer patients regarding the increased metastasis. While the diagnosis and treatments are mostly interrupted during the outbreak, cancer patients may suffer more and need urgent attention in the means of routine controls and prevention of therapy delays. SARS-CoV-2 infected cancer patients are suggested to have more severe forms of the disease and more vulnerable to death comparing to the non-cancer patients mostly due to not only the immune suppressive phenotype regarding with cancer itself or chemotherapy treatments, but also the increased age, addition of other comorbid diseases, immobility, poor performance and degreased nutrition[8]. The severity of the Covid-19 disease has been attributed to the pre-existing, pro-inflammatory and immunosuppressing course seen in cancer patients with the influence of immunosenescence, metabolic syndrome and immune suppressing status such as lymphopenia which diminish or cause abnormalities in the immune response[9-10]. A recent multi-omics study has evaluated more than 120 000 immune biomolecules in different stages of Covid-19 disease and healthy subjects and pictured how immune cells had multifunctional effects on the disease course even without any comorbidity and therefore cancer[11]. Even though it is expected that viral infections are coupled with inflammation and immune response, the increased signaling events, diverse metabolite and cellular particles in

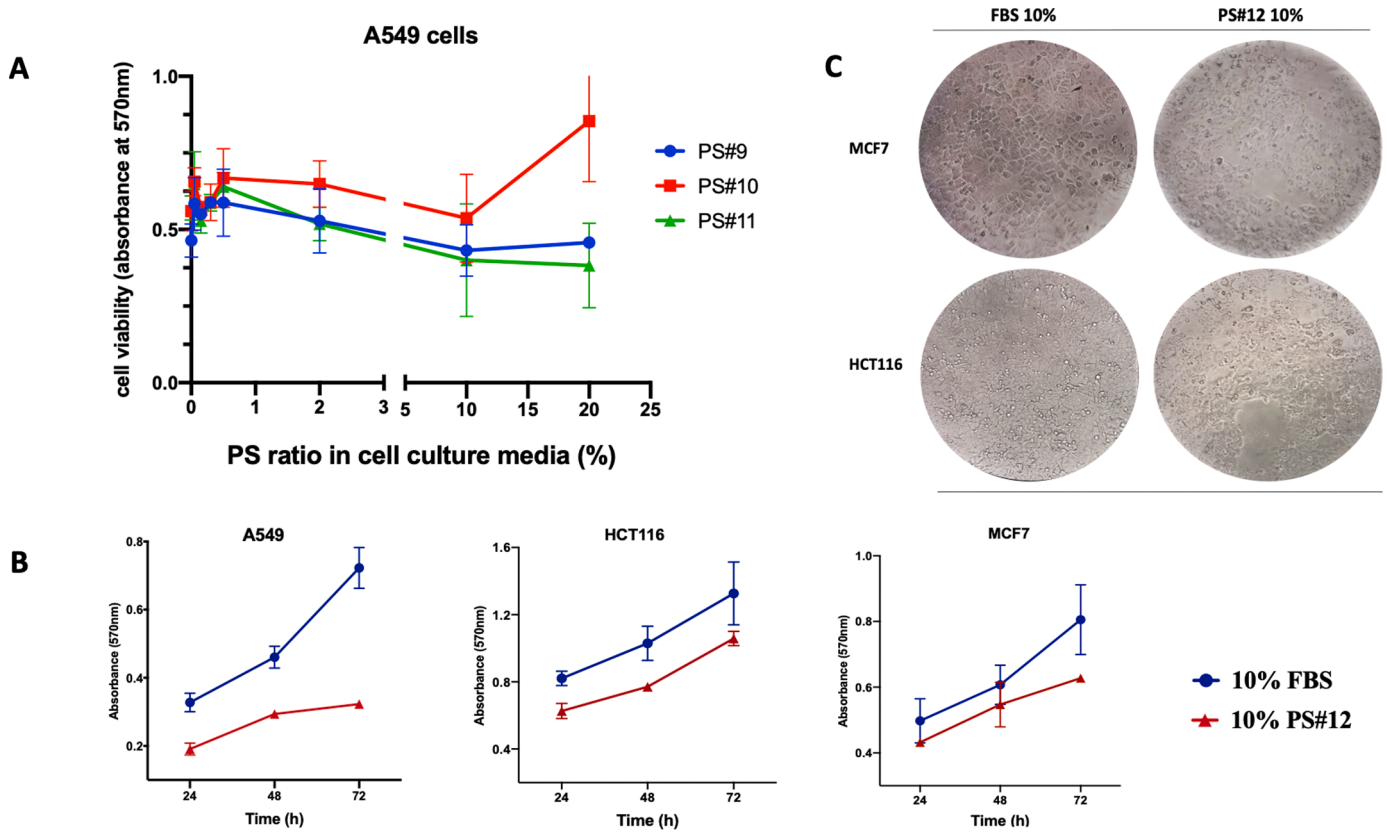

Fig. 4. Effects of PS on cell proliferation and morphology. More PS (PS#9, PS#10 and PS#11) were used to evaluate the effect of PS on cell proliferation first on A549 cells (upper left graph) for 24 h and only one of them increased the number of viable cells at 20% concentration (**A**). Then, PS#12 was given to 3 different cell lines at 10% concentration which the absorbance ratio at 24, 48 and 72 h time-points were compared with FBS treated cells (**B**). Cell images of HCT116 and MCF7 were obtained at 48th hour (**C**) that show the loose of cell to cell connection in PS#12 treated cells.

Table 2
List of hospitalized Covid-19 patients that also have cancer between 1 April to 1 September 2020.

Cancer-Covid Patients #	Age	Gender	Type of cancer	Stage	Covid-19 outcome	Thorax BT image - 6 months after Covid-19
CCP1	70	Female	Pancreatic carcinoma	IV	Died on the 15th day of hospitalization	–
CCP2	65	Female	Cervix Cancer	IV	Discharged	Increased metastatic nodules in the lungs
CCP3	63	Male	Lung cancer	II	Discharged	unknown
CCP4	68	Female	Lung Cancer	IV	Died on the 11th day of hospitalization	–
CCP5	65	Female	Cholangiocarcinoma	IV	Died on the 3rd day of hospitalization	–
CCP6	57	Female	Gastric cancer	IV	Died on the 3rd day of hospitalization	–
CCP7	43	Male	Lung cancer	IV	Died on the 9th day of hospitalization	–
CCP8	79	Male	Maling melanoma	IV	Discharged	Increased metastatic nodules in the lungs

CCP: Covid-Cancer Patients (CCP8 is the same patient with PS#3).

the serum and/or plasma of the Covid-19 patients as well as genotype differences between individuals and populations, requires more focus to further understand and overcome the morbidity and mortality of the current pandemics. The results of this study indicate that the integrated approach should be considered to understand the underlying mechanisms in SARS-CoV-2 infected cancer patients.

CRediT authorship contribution statement

Yasemin Saygideger: Conceptualization, Methodology, Supervision, Funding acquisition, Writing – original draft. **Aycan Sezan:** Investigation, Project administration, Writing – original draft. **Aslihan Candevir:** Software, Writing – original draft, Formal analysis. **Burcu >Saygıdeğer Demir:** Data curation, Visualization, Resources, Software. **Efraim Güzel, Suheyla Komur, Ferit Kuscu, Ezgi Ozyılmaz, Sedat Kuleci** and **Oya Baydar:** Data curation, Formal analysis. **Ezgi Derinoz:** Validation, Formal analysis. **Ismail Hanta, Hikmet Akkız** and **Yesim Tasova:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

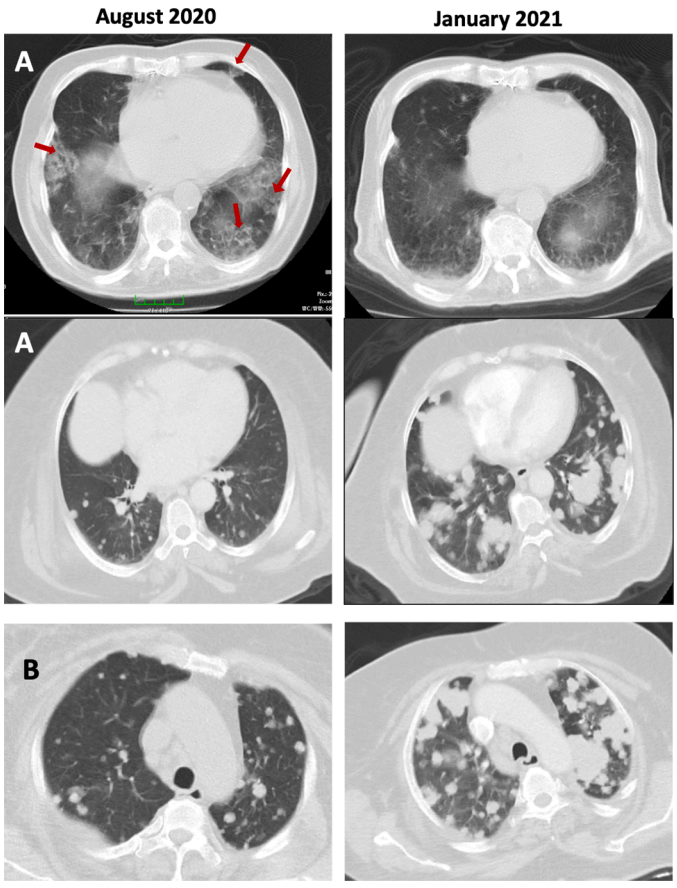

Fig. 5. Thoracic CT Images of two cancer patients on the 6th month of Covid-19. The patients were hospitalized due to Covid-19 pneumonia in August 2020 and discharged after treatment. They admitted to the hospital in January 2021 in order to complications and consequences of cancer. CT images of patient with label A (CP#8 in Table-II) has malign Melanoma and B (CP#2) has cervix carcinoma. Both patients had increased metastatic nodules in January 2021 comparing to August 2020. Red arrows on the upper left images show ground glass opacities of the patient at the time of Covid-19 diagnosis. Note that images A also belongs to the patient PS#3 in Figs. 2 and 3.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2021.100406.

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