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COVID-19 and cancer: A comparative case series

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ABSTRACT

Background: Cancer patients, with an incidence of more than 18 million new cases per year, may constitute a significant portion of the COVID-19 infected population. In the pandemic situation, these patients are considered highly vulnerable to infectious complications due to their immunocompromised state.
Material & Methods: In this retrospective case series, the documents of solid cancer patients infected by SARS-CoV-2, hospitalized in Shariati hospital between 20 February and 20 April 2020, were evaluated. The diagnosis of COVID-19 was based on laboratory-confirmed COVID-19 and/or features of chest CT scan highly suggestive for SARS-CoV-2.
Results: A total of 33 COVID-19-infected cancer patients were included. Mean age was 63.9 years, and 54.5% of the patients were male. LDH level was significantly higher (1487.5 ± 1392.8 vs. 932.3 ± 324.7 U/L, P-value=0.016) and also serum albumin was significantly lower in non-survivors (3.6 ± 0.5 vs. 2.9 ± 0.6 g/dL, p-value=0.03). Among 16 patients with stage IV cancer, thirteen patients died, which was significantly higher compared to stage I-III cancer patients (81.3% vs. 18.8% P-value= <0.001). In terms of developing complications, sepsis, invasive ventilation and mortality was significantly higher in patients who received cytotoxic chemotherapy within the last 14 days.
Conclusion: In this study, we showed that the mortality rate among cancer patients affected by COVID-19 was higher than general population and this rate has a significant correlation with factors including the stage of the disease, the type of cancer, the activity of cancer and finally receiving cytotoxic chemotherapy within 14 days before diagnosis of COVID-19.

Abbreviations and Symbols

COVID-19: Coronavirus Disease 2019
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
RT-PCR: Reverse transcription-polymerase chain reaction
ICU: Intensive care unit
COPD: Chronic obstructive pulmonary disease
ARDS: Acute respiratory distress syndrome
AMI: Acute myocardial infarction
PTE: Pulmonary thromboembolism

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) within the viral background of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), which is a novel single-stranded enveloped RNA virus, was first reported in the city of Wuhan, China in December 2019 [1].

Until now, six coronaviruses have been known to infect humans, including two aggressive strains, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), with a fatality rate of about 10% and 34%, respectively [2, 3]. However, the fatality rate of SARS-COV-2 in China, has been reported to be 2.3% with a high transmission rate [4]. Accordingly, World Health Organization (WHO) declared COVID-19 as a public health emergency with international

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concern. As of June 2020, this virus has affected more than 216 countries, infecting more than 8242,999 individuals and causing over 445, 535 deaths [5].

Cancer patients, with an incidence of more than 18 million new cases per year, may constitute a significant portion of the COVID-19 infected population [6]. In the pandemic situation, these patients are considered highly vulnerable to infectious complications due to their immunocompromised state [7]. Moreover, advanced age, poor functional status and frequent hospital visits, could increase the morbidity and mortality of COVID-19 in cancer patients [8].

Therefore, it is imperative to clear the clinical course and the outcomes of cancer patients infected by COVID-19, and the safety of receiving antineoplastic treatments as usual in the outbreak period. In this retrospective case study, we presented the clinical data, laboratory features and outcomes of hospitalized COVID-19 cancer patients.

Material and methods

Study design and participants

In this retrospective case series, the documents of solid cancer patients infected by SARS-CoV-2, hospitalized in Shariati hospital (a tertiary care referral center designated for COVID-19 patients, affiliated by Tehran University of Medical Sciences) between 20 February and 20 April 2020, were evaluated. This study was by the Ethics committee of Tehran University of Medical Sciences. All patients filled an informed written consent form.

The diagnosis of COVID-19 was based on a positive real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 nucleic acids from nasal and/or pharyngeal specimens and/or features of chest CT scan highly suggestive for SARS-CoV-2 (i.e. the presence of ground glass opacities (GGO), typically with a peripheral and subpleural distribution)[9]. Patients were hospitalized according to the following criteria: prolonged fever (>5 days), respiratory distress (respiratory rate >24 breaths/min), hypoxia (oxygen saturation ≤94% at rest) and hypotension (systolic blood pressure ≤90 mmHg) [2].

Severe clinical events were defined as intensive care unit (ICU) admission, mechanical ventilation necessity, or death[10]. Clinical features, laboratory findings, and chest computed tomography (CT) images were collected. Moreover, history of antineoplastic treatments and comorbidities of the patients, including chronic obstructive pulmonary disease (COPD), hypertension, and diabetes mellitus (DM), were recorded.

Statistical analysis

For descriptive analysis, continuous variables were presented as the mean with standard deviation as appropriate. Categorical variables are presented as number (%). The Shapiro Wilk test was used to test the normality of data distribution. The $\chi 2$ test or Fisher's exact test was used for analysis of categorical data, and the Student *t*-test or Mann-Whitney U test were used for continuous data. All statistical analysis was carried out using SPSS Statistics version 26.0 (IBM, New York, NY). A two-side P-value <0.05 was considered statistically significant.

Results

Between 20 February to 20 April 2020, out of a total of 580 patients admitted in specialized ward for COVID-19 of Shariati hospital, 33 patients had a history of solid cancers (5.68%). Among these, 11 patients had a positive RT-PCR for SARS-CoV-2 and 22 patients had highly suggestive chest CT scan findings in favor of SARS-CoV-2 but negative RT-PCR . The mean age of the patients was 63.9 years, and 54.5% of the patients were males. Age and sex of the patients did not correlate with mortality (P-value=0.312 and 0.22 respectively). Demographic and clinical features of these patients are summarised in Table 1.

Table 1
Demographic and laboratory data in the patients.

	Total *N* = 33	Survivors *N* = 17	non-survivors *N* = 16	P value
Age, years	63.9 ± 11.98	66.9 ± 12.8	60.7 ± 10.5	> 0.05
Interval from fever onset to dyspnea onset (day)	4.1 ± 4.1	4.69 ± 3.75	3 ± 4.86	> 0.05
Symptoms and signs at on admission				
Fever	20 (60.6)	13 (76.5)	7 (43.8)	> 0.05
Cough	16 (48.5)	9 (52.9)	7 (43.8)	> 0.05
Serum Biomarkers				
WBC count, $10^3/\mu L$	10.2 ± 7.8	10.1 ± 8.1	10.3 ± 7.6	> 0.05
Hb, g/dl	11.9 ± 3.1	12.1 ± 3.3	11.8 ± 3.	> 0.05
RDW	14.7 ± 2.8	14.6 ± 2.5	14.9 ± 2.9	> 0.05
Neutrophil × $10^9/L$	8.4 ± 7.3	7.8 ± 7.9	8.9 ± 6.8	> 0.05
Lymphocyte × $10^9/L$	0.87±0.82	0.88±0.71	0.86±0.94	> 0.05
Platelet × $10^9/L$	176±138	209±152	140±116	> 0.05
Neutrophil-to-lymphocyte ratio (NLR)	12.9 ± 11.7	10.9 ± 9.5	15±13.7	> 0.05
Lymphocyte-to-C-reactive protein ratio (LCR)	42.9 ± 154.8	65.2 ± 214.8	19.3 ± 26.9	> 0.05
Platelet-to-lymphocyte ratio (PLR)	587.8 ± 1478.5	817.5 ± 2024.1	343.8 ± 412.1	> 0.05
Serum Albumin (g/dL)	3.2 ± 0.7	3.6 ± 0.5	2.9 ± 0.6	0.03
LDH (U/L)	1487.5 ± 1392.8	932.3 ± 324.7	2077±1818	0.016
ESR (mm/hr)	69.1 ± 34.9	64.1 ± 34.5	77.4 ± 35.7	> 0.05
CRP (mg/L)	90.2 ± 58.7	97.6 ± 68.4	82.3 ± 46.8	> 0.05

Data in are presented as No. (%) or Mean ± SD.

Regarding to laboratory findings, blood count results, at the time of admission showed anemia (i.e. Hb<12 mg/dl) in 26 (78.78%) patients, lymphocytopenia (absolute lymphocyte count <1000/microL) in 23 (69.69%) and thrombocytopenia (platelet count Less than 150,000/microL) in 14 (42.42%) patients. Mean Neutrophil-to-lymphocyte ratio (NLR) was 12.9. Elevated erythrocyte sedimentation rate (i.e., > 30 mm/hour) was found in 27 patients (81.81%), high C-reactive protein (i.e., > 10 mg/L) levels in 31 patients (93.93%), high levels of lactate dehydrogenase (i.e., > 280 unit/L) in 30 patients (90.90%) and low levels of serum albumin (i.e., < 3.5 g/dl) in 29 patients (87.87%).

There was no difference in COVID-19 symptoms, lymphocytopenia, thrombocytopenia between survivors and non-survivors cancer patients. However, LDH level was significantly higher (7170±2077 vs. 932.3 ± 324.7 U/L, P-value=0.016) and also serum albumin was significantly lower in non-survivors (3.6 ± 0.5 vs. 2.9 ± 0.6 g/dL, p-value=0.03). Between two survivors and non-survivors groups PLR (817±2024 vs. 343±412) and NLR (10.9 ± 9.5 vs.15±13.7, respectively) were not significantly different (p-value>0.05).

The mean length of hospitalization was 7.7 days (range 1.0–30.0) and the mean time from the symptoms onset to admission in COVID-19 unit was 4.34 days (range 0–14.0 days).

Mortality rate was significantly higher in 18 patients who received cytotoxic chemotherapy within the last 14 days (72% vs. 20%, P-value: 0.03) and they had also significantly shorter mean time from admission to death compared with 15 patients who undergone cancer treatment more than two weeks before their admission due to COVID-19 or not given cytotoxic chemotherapy within the last 14 days (5.62±4.7 days

vs18.5 ± 16.2 days P-value: 0.02).

In terms of developing complications, although sepsis was significantly higher in patients who received cytotoxic chemotherapy within the last 14 days (50% vs. 13% P-value: 0.026), occurrence of acute respiratory distress syndrome (ARDS), acute myocardial infarction (AMI) and pulmonary thromboembolism (PTE) were not significantly different between the two groups(P-value>0.05) (Fig. 1).

The most frequent cancers were breast cancer ($n = 6$, 18.2%), colon cancer ($n = 6$, 18.2%) and gastric cancer ($n = 6$, 18.2%). Among them, five patients had a history of pulmonary metastasis (table 2). Moreover, four patients (12.12%) had a primary diagnosis of lung cancer. Type of the cancer did not correlate with mortality (P-value=0.5). However, the mortality rate was significantly higher in patients with a history of lung cancer or metastasis to lung compared to other types of cancer (77% vs. 37% P-value = 0.039).

Out of 33 cancer patients, in 16 cases (48.48%) the cancer was in stage IV, at the time of diagnosis. Among 16 patients with stage IV cancer, thirteen patients died, which was significantly higher compared to stage I-III cancer patients (81.3% vs 18.8% P-value <0.001).

It should be noted that 5 patients (15.15%) developed COVID-19 during antitumour therapy in the hospital (nosocomial SARS-COV-2 infection), but none of them experienced mortality.

In addition to cancer, the most frequent coexisting chronic diseases were cardiovascular diseases ($n = 9$,27.3%) and diabetes mellitus ($n = 8$,24.2%). Associated comorbidities did not significantly increase mortality in this patient series (P-value >0.05).

The most common symptoms on admission were dyspnea ($n = 30$, 90.9%), followed by fever ($n = 20$, 60.6%), dry cough ($n = 16$, 48.5%) and gastrointestinal symptoms ($n = 11$, 33.3%). The initiating symptom did not correlate with mortality (P-value>0.05).

Out of the 33 hospitalized patients, 29 (87.9%) received oxygen therapy, 3 (9.1%) received non-invasive ventilation (NIV) and 16 (48.5%) patients received invasive ventilation (IV). The median duration of NIV and IV were 3 days (range 1.0–8.0) and 8 days (range 0.0–14.0), respectively. Fifteen patients (45.5%) were admitted in intensive care unit (ICU). The most common complication was acute respiratory distress syndrome ($n = 9$; 27.3%), followed by sepsis and septic shock ($n = 11$; 33%) and pulmonary thromboembolism ($n = 1$), respectively. In comparison of severe events between the patients who received cytotoxic chemotherapy within 14 days and other patients, sepsis and IV were significantly higher (Fig. 1). Hydroxychloroquine alone was administered in 5 patients and combined with antiviral agents such as lopinavir/ritonavir, ribavirin and oseltamivir in 28 patients. Corticosteroids were administered in 15 patients, mostly in whom suffered from severe events. A total of 17 (51.5%) patients were discharged from the hospital, with a mean hospital stay of 7.5 days (range 5.0–18.0) and 16 patients (48.8%) died with a mean interval of 7.33 days from admission to death.

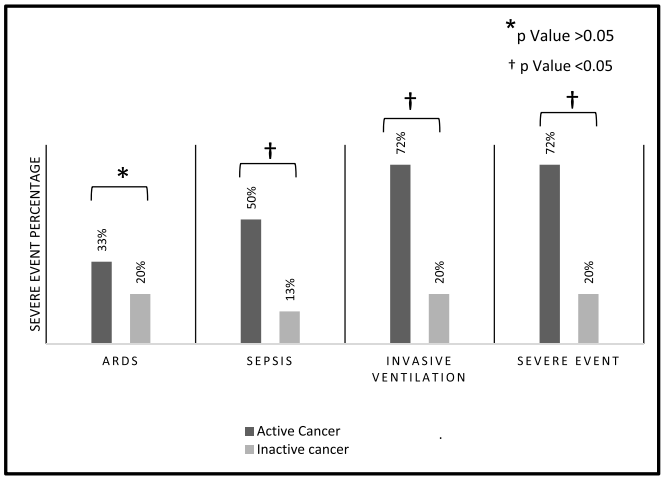

Fig. 1. comparison between covid-19 patients who received cytotoxic chemotherapy within the last 14 days & more than 14 days.

Table 2
Clinical features in survivors vs. non-survivors.

	Total $N = 33$	Survivors $N = 17$	Non-survivors $N = 16$	P value
Mean age ± SD	63.9 ± 11.98	66.9 ± 12.8	60.7 ± 10.5	> 0.05
Tumor diagnosis				
Lung cancer	4 (12.1)	2 (11.8)	2 (11.8)	> 0.05
Breast cancer	6 (18.2)	3 (17.6)	3 (18.8)	> 0.05
Cholangiocarcinoma	1 (3)	0 (0)	1 (6.3)	> 0.05
Colon cancer	6 (18.2)	4 (23.5)	2 (12.5)	> 0.05
Ovarian cancer	3 (9.1)	1 (5.9)	2 (12.5)	> 0.05
Pancreas cancer	2 (6.1)	0	2 (12.5)	> 0.05
Prostate cancer	3 (9.1)	1 (5.9)	2 (12.5)	> 0.05
Stomach cancer	6 (18.2)	5 (29.4)	1 (6.3)	> 0.05
Testis cancer	2 (6.1)	1 (5.9)	1 (6.3)	> 0.05
Tumor stage				
Stage I/II/III	17 (51.5)	14 (82.4)	3 (18.8)	< 0.001
Stage IV	16 (48.5)	3 (17.6)	13 (81.3)	
History of prior treatment				> 0.05
Surgery [a]	3 (9.1)	2 (11.8)	1 (6.3)	> 0.05
Chemo/Radiotherapy [a]	26 (78.8)	12 (70.6)	14 (87.5)	> 0.05
Hormone Therapy [a]	2 (6.1)	2 (11.8)	0	> 0.05
Comorbidities				
Chronic cardiovascular and cerebrovascular disease (including hypertension and coronary heart disease)	9 (27.3)	3 (17.6)	6 (37.5)	> 0.05
Diabetes	8 (24.2)	5 (29.4)	3 (18.8)	> 0.05
Chronic pulmonary disease (including chronic obstructive pulmonary disease and asthma)	5 (15.2)	4 (23.5)	1 (6.3)	> 0.05
Chronic liver disease (including chronic hepatitis B and cirrhosis)	1 (3)	0 (0)	1 (6.3)	> 0.05
cytotoxic chemotherapy within the last 14 days	18 (54.5) versus 15 (45.5)	5 (29.4) versus 12 (70.6)	13 (81.3) versus 3 (18.8)	0.003
Symptoms and signs at on admission				
Fever	20 (60.6)	13 (76.5)	7 (43.8)	> 0.05
Cough	16 (48.5)	9 (52.9)	7 (43.8)	> 0.05
Fatigue	15 (45.5)	7 (41.2)	8 (50)	> 0.05
Dyspnea	30 (90.9)	0 (0)	13 (81.3)	> 0.05
Myalgia	5 (15.2)	3 (17.6)	2 (12.5)	> 0.05
GI symptom	11 (33.3)	6 (35.3)	5 (31.3)	> 0.05

Data in are presented as No. (%) or Mean ± SD.

In this study, there was no significant difference between the two groups of positive and negative SARS-CoV-2 RT-PCR regarding their sex,

age, cancer type, mean Hb concentration, Platelet count, lymphocyte count, serum albumin level, ESR and CRP titer or other laboratory findings and also in terms of clinical symptoms and coexisting (Table 3).

It was also shown that in terms of the mortality rate, there was no significant difference between the two groups of positive and negative SARS-CoV-2 RT-PCR (P-value=0.3).

Discussion

The outbreak of COVID-19 is of international concern and as in other infectious diseases, people with compromised immune systems including the many people with cancer and many more cancer survivors are at increased risk for COVID-19 [11].

Fear and anxiety over the outbreak of COVID-19 have led to a major shift in the provision of cancer care services, with hospitals reducing patient visits and conducting telemedicine specially for breast cancer, colorectal cancer and gynecological cancer [12].

Wang et al. have reported that the proportion of patients with cancer histories has been higher in a cohort with COVID-19 than in the general population in China, and that the patients with cancer were more likely to develop COVID-19 [13]. In our study, 8.1% of the total hospitalized COVID-19 patients had cancer, out of which 48.5% passed away. This rate of mortality was higher than what was reported by Kuderer et al. and the Zhang et al. (13% and 28.6%, respectively) [14,15]. This could be caused by due to the fact that in our hospital patients were admitted according to a strict national guideline and so the mortality rate was higher among all admitted patients.

The findings in this study showed that the most common symptom in hospitalized patients was dyspnea. In general population with COVID-19, fever was known to be the most common symptom, which could be due to the absence of feverish reactions in patients with immune system deficiency. On the other hand, 33.3% of our patients suffered from sepsis and septic shock, which also could be in line for immune deficiency.

Among our cancer patients, those with lung cancer or those with lung metastasis due to non-pulmonary cancers showed a higher mortality rate which could be instigated by a decrease in the lung's functional capacity in these patients. This finding was similar to the report by Zhang et al. [14]. study. Dai et al. [6]. also showed that the mortality rate in COVID-19 patients with lung cancer was higher than other cancers and that the stage of cancer had a direct correlation with mortality. In contrast, Lee study[16] reported no increased mortality rate in patients with lung cancer, compared with the remaining population with cancer and COVID-19, suggesting that patients with lung cancer are not a specifically susceptible group.

In our series, in patients with stage IV cancer, mortality and severe events were observed more frequently compared those with stage I-III. However, Zhang et al. found no significant correlation between the rate of severe events and the stage of cancer [14]. In terms of life-threatening complications, the rate of ARDS in our patients was higher than in the meta-analysis reported by Hu et al. [17].

We found that the mortality rate was significantly higher among the patients with active cancer who had undergone cytotoxic chemotherapy less than 14 days prior to being admitted due to COVID-19, in comparison with the patients who did not have an active cancer and were not on recent cytotoxic therapies. This finding is similar to the report by Zhang et al. [14]. However, Kuderer et al. [15]. found no significant difference between undergoing cytotoxic chemotherapy within 30 days prior to COVID-19 diagnosis and its consequential mortality rate [15]. The results of our study contradict Lee study[18] that found mortality from COVID-19 in cancer patients on cytotoxic chemotherapy or other anticancer treatment are similar with those not on active treatment.

Regarding to the previously conducted studies which reported the sensitivity of chest CT scan for diagnosis of COVID-19 to be 97% [19], we included the cancer patients who had negative RT-PCR for COVID-19 but with highly suggestive chest CT scan findings, in our study. There was no significant difference between the demographic features of these patients and those with positive RT-PCR. Moreover, no difference was observed in terms of outcomes and mortality, except that the rate of ARDS and the need for invasive mechanical ventilation, which were significantly higher in former group, probably due to the primary pulmonary involvement in these patients. Considering the mentioned findings, one can conclude that the in COVID-19 suspected cancer patients, therapeutic measures should be initiated promptly, regardless of RT-PCR results.

In our study, 84.4% and 45.5% of the patients were prescribed at least one antiviral agent and dexamethasone, respectively in early phase of pandemic. However, currently there is no drug that has proven to be effective against SARS-CoV-2.

Results of the SOLIDARITY trial on repurposed antivirals had shown that these agents had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay [20].

Systemic steroids remain controversial in the treatment of viral pneumonia. Recent study by the RECOVERY Collaborative Group showed the use of dexamethasone has protective effect among moderate to severe covid-19 patients who were receiving either invasive mechanical ventilation or oxygen alone [21].

Knowledge from these studies and others like them, had since informed the management of COVID-19 resulting in changes in the care of patients and possibly their outcomes.

This study evaluated the clinical futures and outcome of cancer patients affected by COVID-19 during early phase the current −19 pandemic wherein healthcare teams grappled with the challenge of managing this infection. The result of this study including the clinical feature, treatment and the outcome of the patients could be compared with studies conducted in next phases of COVID-19 pandemic to better understand the difference between these phases.

Table 3
Comparison of characteristics of patients with positive or negative RT-PCR.

	Positive PCR(n = 11)	Negative PCR(n = 22)	P Value
Age, years	59.8±.16.9	65.9±.8.3	>0.05
Sex, n (%)			
Male	7 (63.6)	11 (50)	>0.05
Female	4 (36.4)	11 (50)	
Serum Biomarker			
ESR(mm/hr)	66.8 ± 37.1	70.3 ± 34.6	>0.05
CRP (mg/L)	73 ± 35.7	98.8 ± 66.4	>0.05
NLR	13.5 ± 13.4	12.6 ± 11.1	>0.05
LCR	98.9 ± 265.1	14.9 ± 23.8	>0.05
Albumin (g/dL)	3.2 ± 0.65	3.3 ± 0.75	>0.05
LDH (U/L)	1586 ± 1319	1438 ± 1455	>0.05
Admit to Death, days	4.2 ± 2.6	8.4 ± 8.6	>0.05
Length of hospitalization, days	5.45± 3.2	8.8 ± 6.9	>0.05
Symptom to hospital, day	3.2 ± 4.3	4.9 ± 4.1	>0.05
Severe event, n (%)			
ARDS	1(9.1)	8(36.4)	>0.05
Sepsis	2(18.2)	9(40.9)	>0.05
Invasive Ventilation	4(36.4)	12(54.5)	>0.05
ICU Admission	4(36.4)	11(50)	>0.05
Death	4(36.4)	12(54.5)	>0.05

Data in are presented as No. (%) or Mean ± SD.
NLR: Neutrophil to Lymphocyte ratio, CRP: C - reactive protein, ESR: Erythrocyte Sedimentation Rate, LCR: Lymphocyte to CRP Ratio. ARDS, acute respiratory distress syndrome.

Conclusion

In this study, we showed that the mortality rate among cancer patients affected by COVID-19 was higher than general population and this rate has a significant correlation with factors such as the stage of the disease, the type of cancer, the activity of cancer and finally receiving

cytotoxic chemotherapy within 14 days before diagnosis of COVID-19. We also showed that the outcome of cancer patients with positive RT-PCR for COVID-19 is similar to those with negative RT-PCR with highly suggestive chest CT scan findings.

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None

Ethics approval and consent to participate

This study was approved under the registration number: IR TUMS. VCR.REC 1399–395, by the Ethics committee of Tehran University of Medical Sciences. All patients filled an informed written consent form.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request

Consent

This study was approved under the registration number: IR TUMS. VCR.REC 1399–395, by the Ethics committee of Tehran University of Medical Sciences. All patients filled an informed written consent form.

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.

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