Brief communication

A possible protective role for Bacillus Calmette-Guérin therapy in urinary bladder cancer in the era of COVID-19: a brief report

Given the systemic immunogenic effects of Bacillus Calmette-Guérin (BCG) therapy in patients with bladder cancer and its non-specific immunogenic effects in viral respiratory diseases, we aimed to study severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in bladder cancer patients with a history of BCG therapy. In the present study, all bladder cancer survivors with a history of BCG therapy were identified and included in the study according to the data recovered from the UORC (Uro-Oncology Research Center) registry database. These patients were followed up in terms of acquiring coronavirus disease 2019 (COVID-19). Among the studied patients, 102 eligible bladder cancer patients with a history of BCG therapy entered the study. The males constituted the majority of the patients (86.3%), and more than half of the study population (55.9%) were above 65 years old. Among the understudy patients, 12.7% were confirmed for COVID-19. The study results did not show a statistically significant association between the time and number of BCG therapy courses and SARS-CoV-2 infection. Although no statistically significant association was observed between receiving BCG therapy and developing COVID-19, the infection rate in patients who had recently received BCG therapy was lower than those who had received therapy more than a year ago.

Keywords: Urinary bladder neoplasms, BCG therapy, COVID-19

The unprecedented coronavirus disease 2019 (COVID-19) pandemic, which began in Wuhan, China, has contaminated more than a hundred million of individuals globally with over a million confirmed deaths (February 2021). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in charge of the present pandemic is reputed by the most potent member of the coronavirus family in terms of contagiousness [1]. Evidence attributes the pathogenesis of COVID-19 to cytokine overproduction and the consequent “cytokine storm” leading to lung tissue damage [2]. To date, the number of proposed vaccines against SARS-CoV-2 with different platforms exceed 180, including the “conventional” approach (dead/inactive virus vaccine), authorized vaccines (recombinant protein and vector vaccines), and non-authorized vaccines (RNA and DNA vaccines) [2]. The existing vaccines induce the anti-virus immunological response preventing viral infection.

Bacillus Calmette-Guérin (BCG) vaccine applied for protection against tuberculosis exhibits some degrees of cross-immunity against several bacterial and viral infections [3]. Numerous studies have suggested the existence of the cross-protection capability of BCG vaccination against respiratory infections in rodents as well as human respira-

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Solmaz Ohadian Moghadam1, Behzad Abbasi1, Ali Nowrooz1, Erfan Amini1, Mohammad Reza Nowroozi1, Seyed Ali Momeni1, Hassan Niroomand2

1Uro-Oncology Research Center, Tehran University of Medical Sciences, Tehran; 2Trauma Research Center, AJA University of Medical Sciences, Tehran, Iran

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Corresponding author:
Solmaz Ohadian Moghadam, PhD
Uro-Oncology Research Center, Tehran University of Medical Sciences, Keshavarz Blvd., Tehran, 1419733141, Iran
Tel: +98-21-6643-7969, Fax: +98-21-6643-7969
E-mail: s-ohadian@sina.tums.ac.ir

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tory syncytial virus and human papillomavirus [3-5]. Some evidence underlined significantly higher COVID-19 prevalence and the dissemination intensity in the countries lacking BCG vaccination program [1], proposing a possible protective capability against SARS-CoV-2 infection for this vaccine [6,7]. Although the BCG vaccine does not render direct anti-corona virus characteristics, it presumably endorses the protections against the virus through immune system enhancement [8].

Some evidence has confirmed the improvement of humans’ systemic immunity as well as the protective association against cytokine storm—the leading cause of death in patients diagnosed with SARS-CoV-2 infection—, after intravesical BCG injection, raising the question of whether non-muscle invasive bladder cancer (NMIBC) patients benefit from hypothetical anti-COVID protection following intravesical BCG immunotherapy or not.

We aimed to evaluate COVID-19 status in the subjects undergone BCG therapy for bladder cancer in Iran -a country with a routine BCG vaccination program.

In the present study, the data was extracted from Uro-Oncology Research Center (Tehran, Iran) registry database: surviving bladder cancer patients previously referred to Imam Khomeini General Hospital (Tehran, Iran) were identified, recruited, and further screened/followed for SARS-CoV-2 infection.

The exclusion criteria consisted of the history of previous malignancies rather than bladder cancer and genetic disorders. Patients were surveyed for demographics and history of BCG therapy. Moreover, general clinic-demographic information of each patient (including age, sex, family history of cancer, alcohol consumption, smoking, diabetes, hypertension, body mass index, grade and stage of the tumor, and type of treatment) was recorded using a questionnaire and medical records in patients’ files. Written signed consent was obtained from each participant. This study was approved by the institutional Ethics Committee. All procedures performed in this study were in accordance with the relevant guidelines and regulations and the work was accepted by the Tehran University of Medical Sciences Ethics Committee (IRTUMS. VCR.REC.1399.071).

Among the studied patients, 102 eligible bladder cancer patients with a history of BCG therapy entered the study. The clinico-demographic data of the patients are shown in Table 1. The males constituted the majority of the patients (86.3%), and more than half of the study population (55.9%) were above 65 years old. Among the understudy patients, 12.7% were confirmed for COVID-19. Among bladder cancer patients with confirmed COVID-19, 11 were male, and two were female. Moreover, eight of them were below 65 years old, and five were above 65 years old. Other characteristics of patients with confirmed COVID-19 are shown in Fig. 1. The association between clinico-demographic characteristics of patients with acquiring COVID-19 is shown in Table 2. The study results did not show a statistically significant association between the time and number of BCG therapy courses and SARS-CoV-2 infection.

BCG therapy has been used as a successful treatment with a high initial response in the treatment of NMIBC for more than 40 years. However, the exact mechanism of action in the treatment is not known yet [9]. Upon BCG vaccination, the local immune cells (dendritic cells, neutrophils, and macrophages) are activated in the vaccination site and detect pathogens using different pathogen-associated molecular patterns. Toll-like receptors (TLRs), including TLR-2 and TLR-4, play a role in identifying BCG [10,11]. TLR-2 and TLR-

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**Table 1. Frequency of characteristics of studied bladder cancer patients**

| Characteristic | Category | No. (%) |
|---------------|----------|---------|
| Gender        | Male     | 88 (86.3) |
| Age (yr)      | <$65     | 57 (55.9) |
|               | ≥$65     | 45 (44.1) |
| Smoking       | Positive | 28 (27.5) |
|               | Negative | 74 (72.5) |
| Alcohol       | Positive | 2 (2.0) |
|               | Negative | 100 (98.0) |
| Diabetes      | Positive | 23 (22.5) |
|               | Negative | 79 (77.5) |
| Hypertension  | Positive | 36 (35.3) |
|               | Negative | 66 (64.7) |
| Cardiovascular diseases | Positive | 24 (23.5) |
|               | Negative | 78 (76.5) |
| Other diseases (liver, kidney, other cancers) | Positive | 14 (13.7) |
|               | Negative | 88 (86.3) |
| Tumor grade   | High grade | 26 (25.5) |
|               | Low grade | 76 (74.5) |
| No. of BCG administration | <3 courses | 83 (81.4) |
|               | ≥3 courses | 19 (18.6) |
| Exposure      | Positive | 37 (36.3) |
|               | Negative | 65 (63.7) |
| Confirmed COVID-19 | Positive | 13 (12.7) |
|               | Negative | 89 (87.3) |

BCG, Bacillus Calmette-Guérin; COVID-19, coronavirus disease 2019.
4 receptors, present on the cell surface, are activated by viral glycoproteins and initiate antiviral immune system through a TLR-signaling mechanism. After these cells are activated, they produce proinflammatory cytokines [12]. Studies have highlighted the non-specific protective effects of the BCG vaccine against non-tuberculous infections, such as respiratory infection in children, bladder cancer, asthma, and autoimmune diseases such as diabetes type 1 [8].

BCG therapy induces a robust innate immune response, leading to immunity in almost all cases. Studies show that urothelial cells, including bladder cancer cells and immune system cells, contribute to the anti-tumoral response in BCG therapy. Bladder cancer cells attach to the fibronectin in the bladder wall and facilitate the invasion of BCG, secretion of cytokines, and presenting the antigens of cancer cells and BCG to the immune system, and the bladder cancer cells are then killed by the direct cytotoxicity effects of the immune cells [9]. Although the local immunogenic effects of intravesical BCG therapy are often discussed, the systemic immunologic effects of the vaccine have already been ascertained [8]. Some countries, such as India and Japan, have implemented the global BCG immunization program, while in some others, such as Canada, United States, Italy, Spain, etc., this program is implemented only for the high-risk population [1]. However, no documented evidence of the direct association between BCG vaccination and a decreased risk of acquiring COVID-19 has been reported [1,13]. Some studies have reported lower numbers of SARS-CoV-2 infections in countries with BCG vaccination policies [14].

Some trials have been initiated to evaluate the effects of BCG vaccination and the decreased number of COVID-19 cases [15]. The primary evidence on the COVID-19 pandemic shows that the severity and mortality rate of the disease differs in various parts of the world. Therefore, understanding why some populations are more susceptible to this disease would help better control the disease. An observational study has reported different impacts of COVID-19 in various countries and attributed it to the underlying differences in their cultural norms and health infrastructure. They have also highlighted the differences in national BCG vaccination policies for children in this regard, which would lead to extensive protection against respiratory infections. Moreover, the association between BCG vaccination policies of countries and their COVID-19 mortality was compared in the study. They reported that countries without global BCG vaccination policies, such as Italy, the Netherlands, and United States, were affected more by the COVID-19 impacts than other countries with long-term BCG global vaccination policies [8]. Moreover, the countries which started the BCG vaccination with delay (such as Iran, which started the process in 1984) have experienced higher mortality rates [8].

### Table 2. The association between patient characteristics and SARS-CoV-2 infection

| Variable                        | Total | Smoking | No | <3 courses | ≥3 courses | ≥1 year | <1 year |
|---------------------------------|-------|---------|----|------------|------------|---------|---------|
| Confirmed COVID-19 cases        |       |         |    |            |            |         |         |
| Negative                        | 89 (87.3) | 24 (85.7) | 65 (87.8) | 72 (86.7) | 17 (89.5)  | 17 (81.0)  | 72 (88.9) |
| Positive                        | 13 (12.7) | 4 (14.3)  | 9 (12.2)   | 11 (13.3) | 2 (10.5)   | 4 (19.0) | 9 (11.1) |
| p-value<sup>a</sup>             | 0.748 | 0.1     |     | 0.461      |            |         |         |
| RR of acquiring COVID-19 (95% CI)| 1.17 (0.39–3.51) | 1.26 (0.30–5.22) | 1.72 (0.59–5.03) | |

Values are presented as number (%), unless otherwise stated.

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BCG, Bacillus Calmette-Guérin; COVID-19, coronavirus disease 2019; RR, relative risk; CI, confidence interval.

<sup>a</sup>By Fisher’s exact test.

#### Fig. 1. Frequency of different characteristics of bladder cancer patients with confirmed coronavirus disease 2019.


The results of the present study showed that among patients with confirmed COVID-19, 11 (84.6%) had received less than three courses of BCG, and two patients (15%) had received three or more BCG treatment courses. Although a lower percentage of patients who had received more BCG therapy courses developed COVID-19 (10.5% versus 13.3%), no significant association was observed between SARS-CoV-2 infection and the number of BCG therapy courses, meaning that the risk of contracting COVID-19 in patients with more than three courses of BCG therapy was statistically similar to those with fewer BCG therapy courses.

The analyses showed that incidence of COVID-19 was higher in patients with a history of BCG therapy more than a year ago than in those who had recently received BCG therapy (19% versus 11.1%); however, the increased risk was not significant, although it may still indicate a potentially protective effect of BCG administration.

Several studies have been reported on the association between smoking and acquiring COVID-19. On one hand, these studies have suggested that smokers might be at higher risk for SARS-CoV-2 infection due to increased expression of the ACE-2 gene in these patients [16]. Furthermore, a review article has recently examined the effects of smoking on disease severity in COVID-19 and concluded that active smoking and a history of smoking are significantly associated with severe COVID-19 [17]. On the other hand, other epidemiological studies have reported that despite the lack of a significant association between current smoking and severe disease in COVID-19, the prevalence of smokers in COVID-19 patients is very low [18-20]. Examining the history of smoking in the patients in a study in Italy showed that none of the 112 understudy patients were smokers, and only 20% of them had a previous history of smoking [21]. The infection rate among the smokers and non-smokers in our study was 12.2% and 14.3%, respectively. Although the infection rate among the non-smokers was relatively higher, no significant association was observed between smoking and SARS-CoV-2 infection.

Like other studies, the present study had limitations, the most important of which was the cross-sectional design of the low number of samples.

In general, our study results showed that the rate of SARS-CoV-2 infection among patients with bladder cancer was around 13%. Our data show that although the families of some patients had developed COVID-19, even in some cases the severe form, the understudy patients who had received BCG therapy were not inflicted or merely developed a mild disease. Moreover, none of the patients in our study who were infected with SARS-CoV-2 virus were hospitalized and developed severe disease. Although no statistically significant association was observed between receiving BCG therapy and developing COVID-19, the infection rate in patients who had recently received BCG therapy was lower than those who had received therapy more than a year ago. These findings may suggest the possible protective and non-specific immunogenic effect of BCG therapy against SARS-CoV-2. Ultimately, given that BCG vaccination is available and inexpensive, it is suggested that broader clinical trials with a larger sample size be conducted to detect the association between this vaccine and preventing COVID-19 and assessing its possible non-specific immunogenic effects. Furthermore, we recommend that by designing case-control studies, the infection rate and disease severity be compared between patients with a history of BCG therapy and those without.

**ORCID**

Solmaz Ohadian Moghadam  
https://orcid.org/0000-0001-9745-7063

Behzad Abbasi  
https://orcid.org/0000-0002-7175-9984

Ali Nowroozi  
https://orcid.org/0000-0002-7624-5026

Erfan Amini  
https://orcid.org/0000-0001-9647-0047

Mohammad Reza Nowroozi  
https://orcid.org/0000-0002-6306-3426

Seyed Ali Momeni  
https://orcid.org/0000-0002-4995-4150

Hassan Niroomand  
https://orcid.org/0000-0003-3429-6842

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