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Original Article

Can torque teno virus be a predictor of SARS-CoV-2 disease progression in cancer patients?

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ABSTRACT

Introduction: Cancer patients with SARS-CoV-2 infection can experience a broad range of clinical manifestations and outcomes. Previous studies have demonstrated an association between torque teno virus (TTV) load and deficiencies of the immune system. The impact of SARS-CoV-2 and TTV viral loads in cancer patients is unknown.
Methods: In this retrospective study, 157 cancer patients and 191 noncancer controls were analysed for SARS-CoV-2 RNA and TTV DNA presence.
Results: SARS-CoV-2 RNA was detected in 66.2% of cancer patients and in 68.6% of noncancer control subjects. In SARS-CoV-2-positive patients, TTV was detectable in 79.8% of cancer patients, while in controls, TTV was detected in 71.7% of subjects. No statistically significant correlation was found between TTV and SARS-CoV-2 loads in cancer patients. However, the 100-day survival rate in cancer patients who died from COVID-19 was significantly lower in the TTV-positive group than in the TTV-negative group ($P = 0.0475$). In the cancer TTV-positive group, those who died also had a higher load of TTV than those who did not die ($P = 0.0097$).
Conclusions: Our findings indicated that the presence of TTV in nasopharyngeal swabs from cancer patients was related to a higher number of deaths from COVID-19 and to a higher TTV DNA load.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), first appeared in December 2019 in Wuhan (China) [1], and the severity of COVID-19 symptoms and outcomes vary immensely among patients. Predicting disease progression and managing disease symptoms is even more challenging in cancer patients with SARS-CoV-2, since cancer patients were excluded from initial vaccine trials and emerging evidences point that they had diminished immune responses to vaccination [2]. Patients with cancer are known to be more sensitive to infections than healthy people because of anticancer treatments such as chemotherapy, radiotherapy, and immunotherapy. Data on the effects of immunosuppression on COVID-19 outcomes in cancer patients remain limited. These patients may exhibit a defective immune response but are also frequently treated with immunosuppressive drugs that might diminish the harmful hyperinaflmmatory response.

Torque teno virus (TTV) is a small, nonenveloped, single-stranded DNA anellovirus that infects humans early in life [3–5]. The prevalence of TTV in the general population is said to be 90%, and the virus is detectable in peripheral blood, stool, saliva, cerebrospinal fluid, and pharyngeal mucus [6–10]. Previous studies have demonstrated an association between TTV viral load and deficiencies of the immune system due to chronic infections and cancer [11–14]. Additionally, a significant increase in TTV DNA levels has been shown to occur after iatrogenic immunosuppression, and TTV DNA load has therefore been suggested as a surrogate marker of the immunological status of the host [15].

Motivated by these considerations, the objective of this study was to determine whether TTV DNA positivity and viral load could be associated with SARS-CoV-2 RNA load in cancer patients with COVID-19 and to investigate possible associations with clinical parameters to assess the potential clinical value of TTV DNA load as a predictor of disease complications. Improved knowledge will allow us to better manage these cancer patients.

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2. Material and methods

2.1. Patients and specimens

This retrospective single-centre study included 157 cancer patients at the Brazilian National Cancer Institute (INCA), Rio de Janeiro, Brazil, with clinical suspicion of SARS-CoV-2 infection between April 10th, 2020 and April 30th, 2020, early in the COVID-19 pandemic in Rio de Janeiro. Specimens were collected immediately after hospital admission from those patients with COVID-19 symptoms and immediately after clinical suspicion of COVID-19 from those already admitted to the hospital for diverse reasons unrelated to COVID-19. The survival status was established for each COVID-19 patient in July 2020 based on hospital clinical records. Survival was calculated based on the date of diagnosis of COVID-19. The demographic and clinical characteristics, including primary cancer site, clinical stage, use of chemotherapy, surgery, metastatic disease, use of corticosteroids, and serological markers at diagnosis, were obtained from the electronic medical records. A control cohort including 191 healthcare workers (noncancer subjects) with symptoms of SARS-CoV-2 infection was tested concomitantly for SARS-CoV-2 and TTV infection.

This study was approved by the National Commission of Ethics in Research (approval number: CAAE 53571116.4.0000.5274) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was waived due to the retrospective design and considering the urgent need to collect data. Only anonymised data were analysed.

2.2. Procedures

The nasopharyngeal swab was collected and placed into a conical tube containing 2 mL of sterile saline. Both viral RNA and DNA were extracted using a Maxwell® 16 Viral Total Nucleic Acid Purification Kit (Promega) according to the manufacturer's instructions. A volume of 200 μL of each sample was subjected to nucleic acid extraction, yielding an elution volume of 50 μL.

All cDNAs were synthesised using SuperScript® II and Random Primers (Thermo Fisher Scientific). Real-time polymerase chain reaction assays were carried out using the U.S. Centers for Disease Control and Prevention (CDC) reagents and protocol for the N1 region in SARS-CoV-2 (IDT™) [16].

TTV DNA load quantification was carried out with TaqMan real-time PCR targeting a highly conserved segment of the untranslated region (UTR) of the viral genome, as previously detailed [17]. The assay can quantitate all known genetic variants of TTV. PCR amplification and amplicon detection were performed using the ViiA 7 Real-Time PCR System (Thermo Fisher Scientific).

To determine the virus copy numbers per cell, a human single-copy housekeeping gene (RNase P and beta-2 microglobulin) was coamplified by real-time quantitative PCR (RQ-PCR) in parallel with the virus-specific assay (N1 and TTV). Absolute levels in each sample were automatically calculated by comparing the cycle threshold (Ct) value to a validated curve made with serial dilutions of plasmid standard (IDT™).

2.3. Statistical analysis

Analysis of the data was performed using GraphPad Prism version 9.0.0 (GraphPad Software Inc., San Diego, CA). Clinical categorical variables were compared using chi-square. The Shapiro–Wilk test was used to assess the normality of the distribution of variables analysed in this paper. Since the null hypothesis about normality was rejected, Spearman's correlation coefficient was used to assess the strength of the correlation between the variables. The Mann–Whitney *U* test was used for comparisons between two independent groups for nonparametric data. The survival rate between groups was compared by the log rank test. Kaplan–Meier survival curves of those who were or were not infected with TTV DNA were constructed. A *P value* of less than 0.05 was considered statistically significant.

3. Results

Based on different studies involving immunosuppressed patients, that indicated the possibility of using TTV DNA load as a marker for immune status [12,14,18], we addressed the potential clinical use of TTV monitoring in a cohort of cancer patients with COVID-19.

In total, nasopharyngeal swabs from 157 cancer patients and 191 noncancer controls were tested for SARS-CoV-2 RNA and TTV DNA by real-time PCR during the study period. Among the cancer patients (60 males and 97 females), the median age was 57.5 years, and most of them (78.3%) had solid malignancies. Among the noncancer controls, the median age was 43 years and most (75%) were female. The use of corticosteroids was seen in 49 (31.2%) cancer cases. Patients with metastatic disease accounted for 37.6% of the cases. Death from COVID-19 occurred in 35.7% of the cancer patients, but no deaths occurred among noncancer controls. The demographic and clinical characteristics of the different groups are described in detail in Table 1.

SARS-CoV-2 RNA was detected in 104 of the cancer patients (66.2%) (range: 26 copies/10^6 cell to 3×10^9 copies/10^6 cell, median 1,484,313 copies/10^6 cell) and detected in 131 of the noncancer controls (68.6%) (range: 69 copies/10^6 cell to 3×10^9 copies/10^6 cell, median 2,325,767 copies/10^6 cell). The SARS-CoV-2 load was similar in controls and in

Table 1
Demographic and clinical characteristics of the study population.

Characteristic	Cancer patients (%)n = 157	Noncancer controls (%)n = 191	*P* value
Age, wars (median, range)	57.5 (2–85)	43 (28–64)	0.0008
Sex			0.0086
Female	97 (61.8)	143 (74.9)	
Male	60 (382)	48 (25.1)	
COVID-19 diagnosis			0.6421
Yes	104 (662)	131 (68.6)	
No	53 (33.8)	60 (31 A)	
TTV positive			0.1550
Yes	83/104 (79.8)	94/131 (71.8)	
No	21/104 (202)	37/131 (28.2)	
Death			<0.0001
Yes, from COVID-19	56 (35.7)	0 (0)	
Yes, other cause	25 (15.9)	0 (0)	
No	76 (48.4)	191 (100)	
Primary cancer site			NT
Solid tumors	123 (78.3)	NA	
Hematological malignancies	34 (21.7)	NA	
Clinical stage			Ni
I-II	21 (13.4)	NA	
III	27 (172)	NA	
IV	75 (47.8)	NA	
NA/Missing	34 (21.6)	NA	
Metastatic disease			NT
Yes	59 (37.6)	NA	
No	83 (52.9)	NA	
Missing	15 (9.5)	NA	
Use of corticosteroid			NT
Yes	49 (312)	NA	
No	87 (55.4)	NA	
Missing	21 (13.4)	NA	
Use of chemotherapy			NT
Yes	61 (38.9)	NA	
No	96 (61.1)	NA	
Missing	0	NA	
Surgery*			NT
Yes	54 (34 A)	NA	
No	103 (65.6)	NA	
Missing	0	NA	

NA: not applicable. NT: not tested. * within the last 60 days.

patients (Fig. 1).

In the present study, 83 of the 104 SARS-CoV-2-positive patients (79.8%) had detectable TTV in nasopharyngeal swab samples. The TTV DNA copy number ranged between 2×10^1 and 28×10^6 copies/10^6 cells (median 1050 copies/10^6 cells). TTV DNA was detected in 94 of the 131 controls who were COVID-19 positive (71.8%). The range of TTV DNA load was 1.4×10^1 to 16×10^5 copies/10^6 cell (median 173.8 copies/10^6 cell). As shown in Fig. 2, the TTV DNA load was significantly higher in cancer patients than in noncancer controls ($P = 0.0052$).

No statistically significant correlation was found throughout the study period between TTV load and SARS-CoV-2 viral load in cancer patients. Additionally, among patients with COVID-19, when metastatic disease, corticosteroid use, clinical stage and surgery were compared with TTV viral load, no significant difference was found. However, when chemotherapy use in cancer patients with COVID-19 was analysed, interestingly, the TTV load was significantly higher in those who did not receive chemotherapy (median 594.3 copies/10^6 cell vs 162.7 copies/10^6 cell, $P = 0.0435$). In cancer patients COVID-19 negative, this comparison was not significant.

Because a correlation between age and sex with TTV replication has been previously reported in healthy subjects [15], we also tested whether this observation would be reproducible in our study. No correlation between age, sex and TTV infection rate was found in cancer and non-cancer groups. The laboratory data at the time of SARS-CoV-2 diagnosis, including the levels of C-reactive protein and D-dimer, were compared between the TTV DNA-positive and TTV DNA-negative groups, but the differences were not significant.

Furthermore, we determined whether TTV positivity and DNA TTV load found in 104 cancer patients with COVID-19 might be correlated with death. Firstly, four groups were segregated considering the presence of TTV and if cause of death was related to or unrelated with COVID-19 infection. In the group TTV positive, 38.6% of patients had death related to COVID-19 infection, while in the TTV negative group, 19.0% had death related to COVID-19 infection. The 100-day survival rate in cancer patients who died from COVID-19 was significantly lower in the TTV DNA-positive group than in the TTV DNA-negative group ($P = 0.0475$, Fig. 3A), while in cancer patients who died from another cause the difference was not significant ($P = 0.1355$, Fig. 3B). Lastly, in the TTV DNA-positive group, those who died had a higher TTV load than those who did not die (median TTV load 934.5 vs 109.6 copies/10^6 cell, respectively, $P = 0.0097$).

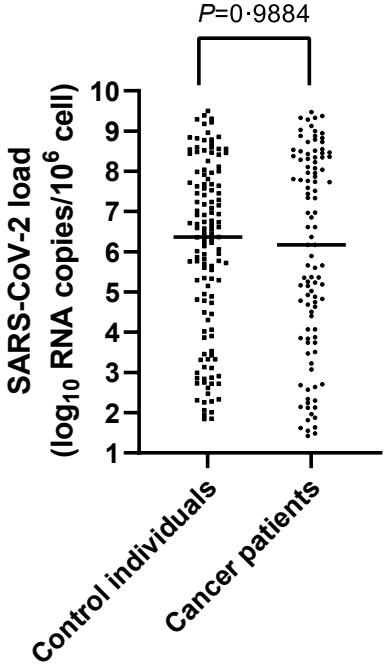

Fig. 1. SARS-CoV-2 RNA load for 131 control individuals and 104 cancer patients. Bars indicating the median values and *P values* for comparisons between groups (Mann–Whitney *U* test) are shown.

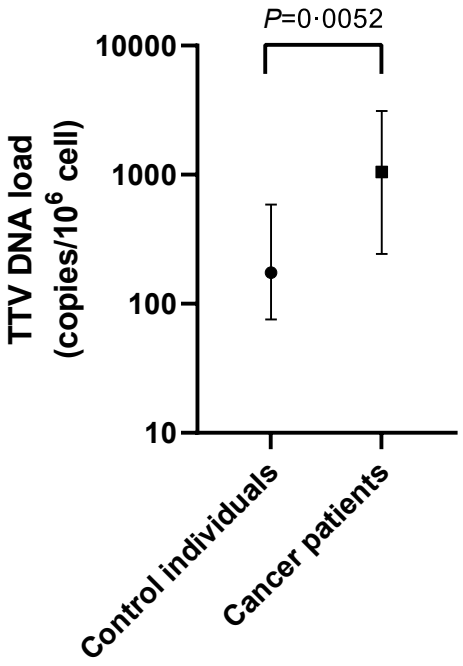

Fig. 2. TTV DNA load for 131 control individuals and 104 cancer patients, both groups with positive diagnoses for SARS-CoV-2. The Mann–Whitney *U* test was performed to compare the median values. The vertical bars represent the median with a 95% confidence interval.

4. Discussion

Development of COVID-19 vaccine and administration of doses have become a global priority since the beginning of the pandemic. However, patients with cancer are still between special populations at higher risk of complications and mortality, if we consider that their seroconversion rates and antibody titres are lower than healthy subjects [2]. Identifying specific risk factors and/or predictors for a severe course of COVID-19 in patients with cancer is of great importance.

TTV was first discovered in Japan in 1997 in five patients with acute posttransfusion non-A to G hepatitis [3]. The viral load of TTV increases under compromised immune response conditions [18], and its kinetics were found to be related to other viruses, such as cytomegalovirus [19] and human BK polyomavirus [20]. As TTV is not sensitive to current antiviral prophylaxis/therapy [21], the number of viral copies may be an appropriate parameter to measure immunosuppression and could represent an additional parameter to identify patients at higher risk for complications following SARS-CoV-2 infection.

Here, we confirmed previous observations that described higher TTV load levels in immunocompromised patients than in immunocompetent controls [4,14,22,23]. We assumed that the impaired immune system in cancer patients might contribute to a high prevalence of TTV. Our findings not only indicated that the presence of TTV in nasopharyngeal swab samples was related to the highest number of deaths from COVID-19 but also revealed a higher TTV copy number in these patients. Unexpectedly, this difference in TTV positivity and load was not related to the use of corticosteroids (which could lower their immunity status) or associated with metastatic disease, clinical stage and surgery. Interestingly, cancer patients who did not receive chemotherapy in the two months prior to a positive diagnosis of COVID-19 had a higher TTV load compared to those who received chemotherapy. More studies are

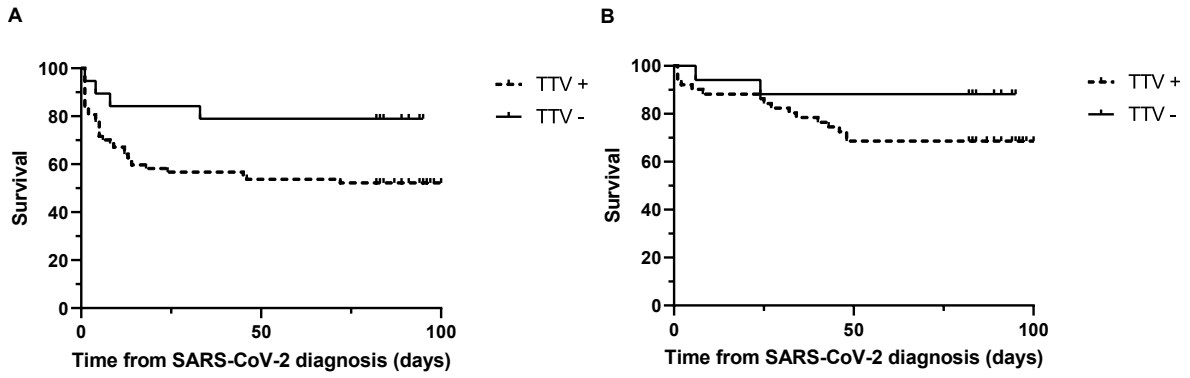

Fig. 3. Survival curves of cancer patients with SARS-CoV-2 who did or did not have TTV DNA in their nasopharyngeal swab sample. Kaplan–Meier survival curves are shown. A. Cancer patients who died from COVID-19 (P = 0.0475). B. Cancer patients who died from another cause (P = 0.1355).

needed to understand this finding.

Although no clear association of TTV with a specific human disease has been found thus far, a direct effect in infection, particularly in immunocompromised patients, cannot be entirely excluded. TTV was detected in nasal brushing samples of children with recurrent or persistent pneumonia [24]. TTV load was associated with airflow limitation within the peripheral airways in children with bronchiectasis or asthma [25,26]. In another study, the detection of TTV was associated with acute respiratory infection and hospitalization, and all TTV-positive acute respiratory infection patients were hospitalised [27].

Regarding COVID-19-related complications, the level of disease severity could be attributed to different factors, such as age, the presence of comorbid health conditions and the viral load of SARS-CoV-2, which was indicated as a potential marker for assessing disease severity and prognosis [28]. The higher the viral load, the more severe the clinical outcomes in patients, who also presented a long virus-shedding period [28]. Here, we examined the nasopharyngeal swab samples of 157 cancer patients with clinical suspicion of COVID-19 and quantified the virus in 104 samples; however, we did not find an association between viral load and risk of death. We also did not find a significant correlation between TTV load and SARS-CoV-2 load in cancer patients. This finding can be explained, at least in part, by the lack of an effect of SARS-CoV-2 RNA load on death in the patient group. We hypothesize that, perhaps both SARS-CoV-2 and TTV might replicate in the nasopharyngeal tract in the same cells and use similar host receptors or that TTV replication suppresses SARS-CoV-2 replication in cancer patients. In addition, earlier studies have shown that in hospitalised patients, inflammatory biomarkers such as C-reactive protein and D-dimer can be used to predict clinical outcomes in COVID-19 patients [29,30]. In this study, we did not find an association between TTV load and these two serological markers.

To our knowledge, this is the first study to investigate whether TTV viral load may be a parameter to predict the occurrence of complications specifically in cancer patients with COVID-19. Measuring nasopharyngeal TTV DNA shedding has advantages, such as being easy to collect, and can be performed on the same material used for the detection of SARS-CoV-2.

The main limitation of this study is its retrospective design, which made it impossible to collect a large number of specimens. The general population of the study was very heterogeneous, with patients with several types of neoplasia and anticancer treatment; different degrees of immunodeficiency in patients with cancer are often attributed to the type of chemotherapy received. Nevertheless, given the potential clinical relevance of our findings, prospective and well-powered studies that can validate or refute our findings are needed.

Authorship statement

VEE conceived and designed the experiments. VEE, BEG, and ATP performed the experiments. VEE and BEG wrote the manuscript. RB and EA provided the necessary reagents for carrying out the experiments. GMF contributed to the figure design and statistical analysis. ATP, BEG, EA, GMF, and RB critically revised the manuscript. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Declaration of competing interest

None.

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