

# A retrospective study on the delay in three different timescales of CT simulation among patients with pediatric cancer in a tertiary hospital

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**Abstract.** Patients with pediatric cancer receive radiotherapy to cure several types of cancer, requiring computed tomography simulation (CT sim) for precise treatment. However, there is currently no suitable framework to reduce the inherent delays in CT sim. The present study aimed to identify the underlying causes of the delays in CT sim regarding three different time periods (duration of patient admission to CT sim, diagnosis to treatment and CT sim to treatment) among patients with pediatric cancer. A total of 58 patients with pediatric cancer who received radiation therapy under anesthesia at King Abdulaziz University Hospital (Jeddah, Saudi Arabia) between 2016 and 2021 (60 months) were included in the current study. The underlying cause of delays regarding three separate time periods was determined according to patient type, diagnosis, therapy type and year of diagnosis. The CT sim processing time averaged 73 days and was received by patients after  $28.96 \pm 28.5$  days. The major delays in terms of frequency and length of duration between different time points such as patient admission and CT sim, interval between diagnosis and treatment, and duration between CT sim and therapy were (mean $\pm$ SD)  $37.13 \pm 29.9$ ,  $58.08 \pm 24.9$  and  $28.15 \pm 7.9$  days, respectively. Machine availability, instability of the patients' medical condition and intensity-modulated radiation therapy (IMRT) caused 66.6% of the delays. In conclusion, outpatients may experience CT sim delays. Machine availability, conditions of patients and IMRT treatment were the major reasons to cause the delay in CT sim. Strategies should be employed to prevent CT sim delays and improve patient experience.

## Introduction

Pediatric cancer is the second most frequent cause of death among children. The most frequently diagnosed cancer types

include leukemia (25%), central nervous system tumors (17%) and lymphoma (16%) (1). Pediatric cancers are rare and the treatment of patients is handled differently from adult cases because the most commonly detected cancers and expected clinical signs in adults differ from those in pediatric patients. It is noteworthy that young children are frequently required to be sedated prior to radiation and the availability and efficacy of medications in their respective dosages are also crucial (2). Radiation therapy, alongside surgery, chemotherapy, bone marrow transplantation, immunological and hormonal therapy, targeted drug therapy, cryoablation and radiofrequency ablation, is one of the therapeutic options for cancer. Radiation therapy employs high doses of radiation to kill cancer cells and shrink tumors. The radiation oncologist usually establishes an individualized treatment plan unique for each patient (2).

Globally, computed tomography simulation (CT sim) operations are susceptible to inevitable delays due to limited resources and the simulator's typical 9-h shift without a break (3-5). In addition, multiple doctors are competing for patients' sim time slots. Despite the availability of this information, there is no structure for reducing delays to enhance patient experience and reduce the burden on patients and caregivers. In general, even a 4-week delay in cancer treatment is connected with a higher number of deaths (6). Minimizing system-level cancer treatment delays may enhance survival of the patients (6).

The present study aimed to identify the underlying cause of the delays in CT sim at three different timepoints, namely duration between patient admission and CT sim, interval between diagnosis and treatment, and time interval between CT sim and therapy. In addition, the  $\chi^2$  test and Welch's t-test were employed to analyze the association between the three timepoints: Receiving patients for CT, CT sim until treatment, and diagnosis until treatment according to patient type, type of treatment, diagnosis and year of diagnosis. By acquiring this information, a good CT sim scheme may be established that may reduce the burden for patients to wait and thus prevent the deterioration of their health.

## Materials and methods

**Patients.** The 58 pediatric cancer patients in this retrospective analysis, whose ages ranged from 2 to 9, were sedated and scheduled for various radiation treatments at three different

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time-points between 2016 and 2021 (60 months); the time between the patient's admission and the CT sim, the time between the diagnosis and treatment, and the time between the CT sim and therapy at King Abdulaziz University (Jeddah, Saudi Arabia). The collected data were divided and categorized by patient type, diagnosis, type of treatment and year of CT sim. In order to determine where the most significant delays occurred, the data were separated into three categories: the duration between patient admission and CT sim, the duration between diagnosis and treatment, and the duration between CT sim and therapy. Each of the aforementioned categories has been further broken down based on the observed issues and the difference in duration of the radiotherapy delays.

**Statistical analysis.** The collected data were analyzed using SPSS (version 23; IBM Corp.). Descriptive statistics characterized numerical data given in terms of means and SD. Welch's t-test was used to determine whether a statistically significant difference was present between the delay and no-delay groups regarding three different time lapses between specific events mentioned above that were measured in days. In addition,  $\chi^2$  tests were used to determine the association of certain demographic variables, such as gender, age and location, for the three different time windows related to CT sim.  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Chart review from 2016-2021.** The present retrospective analysis included 58 sedated pediatric patients 33 male and 25 female patients with cancer with an age range of 2-9 years and an average age of 5.34 years. A total of 36 outpatients were included. The most common diagnoses recorded were acute lymphocytic leukemia for 10 patients (17.2%), followed by rhabdomyosarcoma for 9 patients (15.5%), and the two most common types of treatments were volumetric modulated arc therapy (VIMAT) for 32 patients (39%), followed by the total body irradiation (TBI) for 17 patients (20.7%). The present study is a chart review from 2016 to 2021 (Table I). Data from 2020-2021 were excluded from the beginning of pandemic in March 2020 to April 2021, since CT machines were not available for patients with pediatric cancer during the Covid-19 pandemic.

**Reasons for delay.** In Table II, the reasons for the delay in the admission of patients to CT sim and associated percentages are provided. The duration between patient admission and CT sim had a mean of 23.18 days. The minimum time between patient admission and CT sim was 1 day, while the maximum time was 79 days. For delays of  $\geq 14$  days, the causes were observed and tallied. The rate of delay was 73.8%. Machine availability (31%), patient circumstances, including instability of the patient, patient was in the intensive care unit (ICU) and had been subjected to other operations (31%), and administrative concerns, including open file limitations, communication, coordination and new file regulation (13.8%), were the three most common reasons for delays.

Table III shows the percentages of reasons for delays from CT sim to therapy. The mean time between CT sim and treatment was of  $20.66 \pm 9.3$  days. The reasons for delays of  $\geq 27$  days

Table I. Demographic data of patients with pediatric cancer (n=58).

Item	Value
Age, years	5.34 $\pm$ 1.90 (2-9)
Patient type	
Outpatient (referred to King Abdulaziz University)	36 (62.1)
Inpatient	22 (37.9)
Diagnosis	
Acute lymphocytic leukemia	10 (17.2)
Rhabdomyosarcoma	9 (15.5)
Fanconi	1 (1.7)
Neuroblastoma	7 (12.1)
Medulloblastoma	5 (8.6)
Craniopharyngioma	2 (3.4)
Hodgkin's lymphoma	1 (1.7)
Ependymoma	5 (8.6)
Wilm's tumor	6 (10.3)
Glioma	6 (10.3)
Leukemia	2 (3.4)
Other	4 (6.9)
Type of treatment	
Total body irradiation	17 (20.7)
Volumetric modulated arc therapy	32 (39.0)
3D conformal radiation therapy	14 (17.1)
Intensity-modulated radiation therapy	14 (17.1)
Stereotactic radiosurgery	1 (1.2)
N/A	4 (4.9)
Year of radiation treatment	
2016	2 (3.4)
2017	14 (24.1)
2018	17 (29.3)
2019	17 (29.3)
2021	8 (13.8)

Values are expressed as the mean  $\pm$  SD (range) or n (%).

were also determined. The delay rate was 43.1% determined by the method provided, with the three most common causes of delay including therapy canceled for no reason (10.3%), patient or relative having issues or being uncooperative (12.1%), and the condition of the patient being unstable or at the ICU or other lab procedures being performed (12.1%).

Table IV summarizes the reasons of delays between the diagnosis and delays. The duration of radiation therapy prior to diagnosis ranged from 6 to 144 days, with an average of 48.17 treatment days. The delay rate was 86.2%. For delays of  $\geq 21$  days, the main reason was Machine availability (37.9%), followed by patient instability or other procedures conducted (31.0%), and the arrangement depending on the inpatient team (24.1%).

In summary, the delay rate from receiving the patient to CT sim was 63.8%, the delay rate from CT sim to treatment was 43.1%, and the delay rate from diagnosis to treatment

Table II. Duration from patient admission to CT sim in days (n=58).

Variable	Value
Duration from receiving patients to CT sim, days	23.18±18.80 (1-79)
Total number of patients	58 (100.0)
No delay	21 (36.2)
Reasons for delay ≥14 days	
Machine availability	18 (31.0)
Patient conditions, not stable, intensive care unit, other procedure	18 (31.0)
Administrative-related, open file limitation, communication, coordination, open file new regulation	8 (13.8)
Arrangement dependent on inpatient team	8 (13.8)
Patient relative issues, patient or relative not cooperative	10 (17.2)
Physicians' issues	1 (1.7)
Treatment cancelled for unknown reasons	1 (1.7)

Values are expressed as the mean ± SD (range) or n (%). Sim, simulation.

was 86.2%. Furthermore, statistical analysis revealed that there is a significant difference between duration of delayed and non-delayed CT sim groups of all the three time points including patient admission to CT sim ( $P<0.001$ ), CT sim to treatment ( $P<0.001$ ) and diagnosis to treatment ( $P<0.001$ ).

Regarding the influence of patient characteristics on the proportion of patients who experienced delays and/or no delay in admission to CT sim (Table V), none of the variables had a significant influence according to the  $\chi^2$ -test ( $P<0.05$ ). The years with the highest proportion of delayed patients were 2018 and 2019 with 10 patients (58.8%) in 2019 and with 13 patients (76.5%) in 2018. However, it is noteworthy that in 2016, there was no delay documented. In terms of the time of CT sim until treatment (Table VI), among the four factors assessed, the type of treatment had a significant impact, specifically IMRT with 11 patients, 9 (81.8%) of whom experienced a delay and 2 (18.2%) of whom did not. All other types of treatment had higher no-delay rates. By contrast, only 1/7 (14.3%) patients treated with 3D conformal radiation therapy experienced a delay, while 6 (85.7%) did not, with  $P=0.012$  according to the  $\chi^2$ -test. Furthermore, in the summary of the demographics of the four variables and their association with the number of patients experiencing delays and no delay from diagnosis until treatment (Table VII), there was significance for all types of treatment, with  $P=0.018$  according to the  $\chi^2$ -test. A total of 11 (100%) patients treated with IMRT experienced a delay, followed by 9 (90.0%) patients treated with TBI and 24 (88.9%) patients treated with VIMAT.

Furthermore, Table VIII described the reasons for the delay in CT sim until treatment. Six (54.5%) of the 11 patients who had IMRT were outpatients. These individuals were

Table III. Duration between CT sim and treatment in days (n=58).

Variable	Value
CT sim until treatment, days	20.66±9.30 (1-43)
Total number of patients	58 (100.0)
Non-delayed	33 (56.9)
Reasons for delay ≥27 days	
Machine availability	5 (8.6)
Patient condition, not stable, intensive care unit, other procedure	7 (12.1)
Arrangement dependent on inpatient team	3 (5.2)
Patient relative issues, patient or relative not cooperative	7 (12.1)
Physicians issues	1 (1.7)
Medical physics-related	4 (6.9)
Treatment cancelled for unknown reasons	6 (10.3)
Admission-related	1 (1.7)

Values are expressed as the mean ± SD (range) or n (%). Sim, simulation.

Table IV. Duration between the delay from diagnosis to treatment in days (n=58).

Variable	Value
Diagnosis until treatment, days	48.17±26.50 (6-144)
Total	58 (100.0)
Not-delayed	8 (13.8)
Reasons for delay ≥21 days	
Machine availability	22 (37.9)
Patient conditions, not stable, intensive care unit, other procedure	18 (31.0)
Administrative-related, open file limitation, communication, coordination, open file new regulation	3 (5.2)
Arrangement depend on inpatient team	14 (24.1)
Patient relative issues, patient or relative not cooperative	10 (17.2)
Physicians' issues	1 (1.7)
Medical physics-related	5 (8.6)
Treatment cancelled for unknown reasons	5 (8.6)
Admission-related	1 (1.7)

Values are expressed as the mean ± SD (range) or n (%).

diagnosed with acute lymphocytic leukemia (1 patient), rhabdrosarcoma (2 patients), neuroblastoma (3 patients), medulloblastoma (3 patients), Wilms tumor (1 patient) and glioma (1 patient). The primary reason for the delay was that

Table V. Association between demographic characteristics and delays of CT sim after admission.

Demographics	Total	CT sim after patient admission		P-value
		Delay	No delay	
Total	58	37 (63.8)	21 (36.2)	-
Age, years	58	5.24±1.90	5.52±2.00	0.596
Patient type				0.560
Outpatient (referred to King Abdulaziz University)	36	24 (66.7)	12 (33.3)	
Inpatient	22	13 (59.1)	9 (40.9)	
Type of treatment				0.757
Total body irradiation	10	6 (60.0)	4 (40.0)	
Volumetric modulated arc therapy	27	19 (70.4)	8 (29.6)	
3D conformal radiation therapy	7	3 (42.9)	4 (57.1)	
Intensity-modulated radiation therapy	11	7 (63.6)	4 (36.4)	
Stereotactic radiosurgery	1	1 (100.0)	0 (0.0)	
N/A	2	1 (50.0)	1 (50.0)	
Year of radiation treatment				0.232
2016	2	0 (0.0)	2 (100.0)	
2017	14	8 (57.1)	6 (42.9)	
2018	17	10 (58.8)	7 (41.2)	
2019	17	13 (76.5)	4 (23.5)	
2021	8	6 (75.0)	2 (25.0)	

Values are expressed as the mean ± SD or n (%). Sim, simulation.

Table VI. Association of patient characteristics with the delay from CT sim to treatment.

Demographics	Total	Delay from CT sim to treatment		P-value
		Delay	No delay	
Total	58	25 (43.1)	33 (56.9)	-
Age, years	58	5.08±2.1	5.55±1.8	0.364
Patient type				0.057
Outpatient (referred to King Abdulaziz University)	36	19 (52.8)	17 (47.2)	
Inpatient	22	6 (27.3)	16 (72.7)	
Type of treatment				0.012
Total body irradiation	10	2 (20.0)	8 (80.0)	
Volumetric modulated arc therapy	27	11 (40.7)	16 (59.3)	
3D conformal radiation therapy	7	1 (14.3)	6 (85.7)	
Intensity-modulated radiation therapy	11	9 (81.8)	2 (18.2)	
Stereotactic radiosurgery	1	0 (0.0)	1 (100.0)	
N/A	2	2 (100.0)	0 (0.0)	
Year of radiation treatment				0.223
2016	2	0 (0.0)	2 (100.0)	
2017	14	3 (21.4)	11 (78.6)	
2018	17	9 (52.9)	8 (47.1)	
2019	17	9 (52.9)	8 (47.1)	
2021	8	4 (50.0)	4 (50.0)	

Values are expressed as the mean ± SD or n (%). Sim, simulation.

the patient or a family member having difficulties or being uncooperative, and machine availability, accounting for

36.4% each. The year 2018 had the most delays, accounting for 8 patients (72.7%).

Table VII. Association of patient characteristics with delay from diagnosis to treatment.

Demographics	Total	Delay from diagnosis to treatment		P-value
		Delay	No delay	
Total	58	50 (86.2)	8 (13.8)	-
Age, years	58	5.20±1.90	6.25±1.90	0.152
Patient type				0.449
Outpatient (referred to King Abdulaziz University)	36	32 (88.9)	4 (11.1)	
Inpatient	22	18 (81.8)	4 (18.2)	
Type of treatment				0.018
Total body irradiation	10	9 (90.0)	1 (10.0)	
Volumetric modulated arc therapy	27	24 (88.9)	3 (11.1)	
3D conformal radiation therapy	7	3 (42.9)	4 (57.1)	
Intensity-modulated radiation therapy	11	11 (100.0)	0 (0.0)	
Stereotactic radiosurgery	1	1 (100.0)	0 (0.0)	
Not applicable	2	2 (100.0)	0 (0.0)	
Year of radiation treatment				0.889
2016	2	2 (100.0)	0 (0.0)	
2017	14	11 (78.6)	3 (21.4)	
2018	17	15 (88.2)	2 (11.8)	
2019	17	15 (88.2)	2 (11.8)	
2021	8	7 (87.5)	1 (12.5)	

Values are expressed as the mean ± SD or n (%).

## Discussion

The medical records of 58 patients with pediatric cancer collected between 2016 and 2021 revealed underlying reasons for delays in radiation therapy regarding three different time windows: Receiving patients from admission to the CT sim, CT sim until treatment and diagnosis until treatment.

The initial stage for radiation therapy was receiving patients for CT sim. The majority of the 58 patients who encountered a treatment delay were outpatients. Prior to accepting patients for CT, a consultation was required to assess the medical history of the patient and treatment requirements. The visit includes physical examination, assessment of medical history and medications, and discussion of various options for treatment. CT sim was started once all of these assessments had been carried out. This implies that the patient's condition was a significant factor in the therapy delay. Scheduling and various radiation treatments at the three different time intervals were necessary for quality control, and it was done in an effort to maximize machine use; hence, machine availability (39%) was the most common explanation. Watchorn *et al* (7) found that 61% of all referrals were for CT scans and that the average CT scan delay for emergencies was 6 h and 52 min.

Furthermore, according to Mutic *et al* (8), the therapeutic physicist is responsible for the commissioning and periodic quality assurance of the supporting software and the CT sim process, but the diagnostic physicist can be consulted for assistance. The diagnostic physicist is responsible for maintaining the quality if the CT scanner is in the diagnostic radiology unit. By contrast, the radiation oncology physicist reviews the task

group's recommendations, indicating that the machine's availability depends significantly on the expertise and schedule of the radiooncology staff. Grover *et al* (9) reported that most radiotherapy indications were related to cancer treatment, and that it was impossible to establish a cancer control program without radiotherapy. Radiation therapy uses a variety of machines and equipment, making machine availability an essential aspect of treatment planning. The availability of machines is a significant indicator of a country's economic status. Radiation delivery poses multidimensional difficulties and the challenge pertains to physical resources, human personnel and data shortage. Furthermore, another study by Zubizarreta *et al* (10) underlined that access to existing radiotherapy and care affordability remain a significant challenge. Such access is still limited in numerous regions of the world, particularly in low- and middle-income countries, as Abdel-Wahab *et al* (11) concluded in 2021. Even though Saudi Arabia is a country with a high economic status, the demand for equipment remains a significant issue due to the growing number of patients with cancer.

CT sim to treatment was the second period examined. A decrease in patient delay was observed during this step, with data indicating that only 38 patients were delayed, while 40 patients were not. At this stage, the most prevalent causes of delay were the cancellation of therapy for unexplained reasons (14.6%), patient-related issues (12.2%) and patient condition (11%). A strong emphasis on treatment delay was identified, as 78.6% of patients (n=11/14), were delayed when employing IMRT. Even though IMRT is a common form of radiation therapy, certain caregivers are cautious about using

Table VIII. Patients subjected to intensity-modulated therapy and the reasons for delay from CT sim to treatment (n=11).

Variable	Value
Age, years	4.82±1.7 (2-8)
Patient type	
Out-patient (referred to King Abdulaziz University)	6 (54.5)
In-patient	5 (45.5)
Diagnosis	
Acute lymphocytic leukemia	1 (9.1)
Rhabdomyosarcoma	2 (18.2)
Neuroblastoma	3 (27.3)
Medulloblastoma	3 (27.3)
Wilms tumor	1 (9.1)
Glioma	1 (9.1)
Year	
2017	2 (18.2)
2018	8 (72.7)
2021	1 (9.1)
Reason for CT sim till treatment delay for ≥27 days	
Machine availability	4 (36.4)
Patient conditions, not stable, ICU, other procedure	2 (18.2)
Patient relative issues; patient or relative not cooperative	4 (36.4)
Arrangement depending on in-patient team	3 (27.3)
Medical physics related	1 (9.1)
Administrative related, open file limitation, communication, coordination, open file new regulation	1 (9.1)
Physicians' issues	1 (9.1)
Treatment cancelled for unknown reasons	1 (9.1)

Values are expressed as the mean ± SD (range) or n (%). ICU, intensive care unit.

it on children due to its potentially severe adverse effects such as negative health impacts. In a study by Verellen and Vanhavere (12), the use of more machine monitor units per target dosage was required for IMRT treatments, resulting in a larger integral dosage delivered to the normal tissues of the patient and an increased risk of secondary radiation-induced cancers. According to Bindhu *et al* (13), IMRT is 75% more expensive than 3DCRT or definitive chemoradiotherapy, giving a caregiver second thought to continue this type of radiotherapy. On the other hand, compared to conventional 2D and 3D treatments, Cheung (14) explained that IMRT therapies are more susceptible to geometrical errors because of their more significant dose conformity indices. The precision and stability of the patient immobilization system must be considered when estimating the treatment margin necessary for proper target coverage and adequate standard critical tissue protection (14).

By contrast, IMRT may precisely target the tumor, while sparing the surrounding tissue and increasing the chance of getting cured of cancer without radiation exposure is higher than those with the presence of radiation. According to Sterzing *et al* (15), IMRT enables individualized dose distributions and remarkable organ preservation in the most challenging cases. This was accomplished by increasing the quantity of normal tissue exposed to low doses of radiation. A total of 21 individuals displayed local control and no severe acute or chronic toxicity was detected (15). This may be the reason why there were more delays in CT sim treatment, as most patients and radio-oncologists still favored this method due to its effectiveness and precision in treating cancer.

The last time period examined was that from diagnosis to treatment. This phase had the highest delays recorded, accounting for 73 days of delay. Machine availability (45%) and patient conditions (30.5%) were common reasons for delays. Most of the delays still came from outpatients. All types of treatment exhibited a relative increase in patients experiencing a delay in this stage of radiation therapy and a considerable delay was noticed adequately in individuals undergoing IMRT treatment, which accounted for 14 patients (100%). A diagnosis must be made to provide the precise treatment needed for each patient's situation. Therefore, accumulating these concerns would substantially delay gathering enough data and information to create an accurate diagnosis, thus imposing a delay in acquiring such a diagnosis and providing therapy.

To minimize the delay in CT sim, it would be helpful to categorize patients, whether outpatient department or inpatients, depending on the level of health priority. The priority levels are as follows: i) The patient is stable and a minor delay will not affect their health; ii) the patient is generally stable, they are able to survive with minimal therapeutic modification, tumors are stable but require neoadjuvant therapy and palliative care would significantly improve the health status of the patient; and iii) the patient is unstable and cannot afford to delay therapy that would jeopardize their survival; tumors are rapidly growing and may cause severe illness if not treated immediately. Patients examined and rated to be under priority levels 2 and 3 will have access to be admitted to the CT sim.

Finally, in the present study, quality and safety were the main drivers for subjecting patients to CT sim and there were also previous studies suggesting that a long delay of CT may lead to a decrease of tumor control (16). Patients receiving palliative care usually encounter delays, as they are still gaining relief from current symptoms, leading to a delay in the initiation of radiation treatment and further increasing distant metastasis. A study by Xu *et al* (16) from 2019 identified that the average treatment delay was 8 days. Failure modes also cause delays in treatment initiation. With that, it is important to consider the following: i) Dosimetrists should send contour requests to the physicians right after CT sim with a clear deadline; ii) there should be efficient communication between dosimetrists and physicians for updates on patients' anatomical and clinical reports; iii) there should be better communication with the patient on the treatment progress; and iv) the situation should be clarified with the whole hospital committee to maintain a timely workflow (16).

The present study was limited by the small sample size that was investigated for the time of delay for patients who



underwent CT sim. It was also not possible to study the effect on delays between CT sim and treatment and its effects on the condition of the patient. Further studies are required to address these limitations to provide more efficient results. It is also recommended to test the effects on delays in CT sim, while also determining the performance of the treatment and to measure its efficacy.

CT sims for outpatients will likely be delayed due to the presumption that priority will always be given to in-patients who require greater attention and examination. Machine availability, patient condition and IMRT treatment are CT sim delay considerations. By utilizing approaches and prioritizing patients according to their health status, it is possible to eliminate CT sim delays and poor patient outcomes.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

### Authors' contributions

ADAM and RKAM conceptualized and designed the study, prepared the methodology, executed the investigation, and wrote and edited the final manuscript. RKAM completed the formal analysis. Both authors read and approved the final version of the manuscript. ADAM and RKAM confirm the authenticity of all the raw data.

### Ethics approval and consent to participate

Ethics approval was granted by the ethical board of King Abdulaziz University Hospital (Jeddah, Saudi Arabia; approval no. 338-21). Written informed consent was obtained from each subject who participated in the questionnaire.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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