

## Diagnostic accuracy of sinus tachycardia as an independent clinical indicator among different COVID-19 variants

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**A** – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

**Summary Background.** The most common arrhythmia which have been reported frequently in COVID-19 patients is sinus tachycardia. As COVID-19 is usually misdiagnosed with other respiratory tract diseases, introduction of a rapid clinical indicator for out of proportional sinus tachycardia in the diagnosis of COVID-19 during the early viral replication stage is essential for better cost-effective use of resources.

**Objectives.** This study was conducted to determine the diagnostic accuracy of sinus tachycardia as an independent indicator of COVID-19.

**Material and methods.** This is a cross-sectional analytical study. It included 152 healthcare workers who fulfilled the inclusion criteria. Multiple logistic regression analysis was conducted to investigate the factors associated with COVID-19 among the entire study sample and among each group.

**Results.** Among our participants, 32.9% were male, while 67.1% were female, with a mean age of  $35.47 \pm 7.09$  years. It was found that 51.3% of our sample were COVID-19 PCR positive, and the mean number of days of symptoms at presentation was  $2.01 \pm 1.29$ . It was found that the prevalence of out of proportional sinus tachycardia among the participants diagnosed with COVID-19 in 2021 was triple that of the participants who were recruited in 2020 (61%, 26%, respectively). It was found that there was significant association between pulse rate and COVID-19, with gender, age, temperature or days of symptoms having no effect.

**Conclusions.** The study highlights the diagnostic accuracy of sinus tachycardia as an independent indicator of COVID-19, especially the Omicron variant, as a higher pulse rate is associated with higher odds of having COVID-19

**Key words:** sinus tachycardia, COVID-19, cardiac arrhythmias.

Elamary M, Alomari FK, Newera A, Selim E, Manalus MC, Laureta JMC, Tossion EE. Diagnostic accuracy of sinus tachycardia as an independent clinical indicator among different COVID-19 variants. *Fam Med Prim Care Rev* 2023; 25(1): 29–35, doi: <https://doi.org/10.5114/fmprcr.2023.125489>.

### Background

At the end of 2019, a novel coronavirus was identified as the cause of pneumonia cases in Wuhan, China, which rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world [1]. This first outbreak of the novel coronavirus was declared as a public health emergency of international concern by the World Health Organization on 30 January [2] and a global pandemic on 11 March 2020 [1]. The COVID-19 pandemic spread rapidly around the world, including Saudi Arabia, which led to a severe health emergency [3].

Different variants of COVID-19 have been discovered worldwide, the latest variant being SARS-CoV-2 Omicron (B.1.1.529),

which is the most heavily muted strain discovered so far in one of the provinces in South Africa on 24 November 2021 and has been declared by the World Health Organization (WHO) as the fifth Variant of Concern (VOC) after the Alpha, Beta, Gamma, and Delta variants on 26 November 2021 [4].

Following South Africa, more than 150 countries had been detected with the Omicron variant as of 20 January 2022 [5], and the United Kingdom reported the first known death of a patient with the Omicron variant [6]. Among patients with symptomatic COVID-19, cough, myalgias and headache are the most commonly reported symptoms. Other features, including diarrhoea, sore throat and abnormalities concerning smell or taste, have also been described. Mild upper respiratory symptoms (e.g. nasal congestion, sneezing) appear to be more common



with the Omicron variant [7], whereas low oxygen saturation, abnormal pulse rates and shortness of breath are frequently reported symptoms for the Delta variant [8]. Although COVID-19 symptoms due to the Omicron variant are milder so far, this could potentially raise death rates as it is highly contagious [9].

Studies concerning the accuracy of signs and symptoms showed that a combination of  $\geq 2$  symptoms/signs (fever, cough, anosmia, dyspnoea, oxygen saturation  $< 93\%$ , headache) results in a highly sensitivity model for quick and accurate diagnosis of COVID-19 [10]. Early studies suggest that COVID-19 is associated with a high incidence of cardiac arrhythmias. Severe acute respiratory syndrome due to COVID-19 may cause injury to cardiac myocytes, leading to myocarditis, and may increase the risk of arrhythmia [11]. Myocarditis is an inflammatory disease of the heart which occurs due to inflammatory infiltrates and myocardial injury without an ischemic cause [12]. The most common cause of myocarditis in the United States and other developed countries is viral infection [13]. The most common arrhythmia overall in patients with COVID-19 is sinus tachycardia, but the most likely pathologic arrhythmias include atrial fibrillation, atrial flutter and monomorphic or polymorphic ventricular tachycardia [14]. Sinus tachycardia can occur as an attribution to elevated temperature in adults (approximately 8.5 beats/minute for every  $1^{\circ}\text{C}$  elevation in oral temperature above  $37.8^{\circ}\text{C}$ ) [15, 16]. If fever is felt to be the cause of tachycardia, then the elevated heart rate should resolve when the temperature returns to normal, and this should point towards another reason for sinus tachycardia other than fever in individuals who present with tachycardia and who are afebrile, even if there was recent history of fever [17]. Few studies have fully described the diagnostic accuracy of sinus tachycardia as a clinical indicator for suspected COVID-19, and no comparison has been made in this field between different COVID-19 variants [18].

Considering that the specificity and sensitivity of signs and symptoms of different COVID-19 variants help direct the patient towards appropriate covid testing, especially as the new emerging Omicron variant is very similar to many respiratory tract infections, the more accurate a clinical indicator to suspect covid is, the less unnecessary testing will be done.

Furthermore, we do not have enough epidemiological data regarding the addition of sinus tachycardia out of proportion to fever to the classical criteria used to differentiate between the Omicron variant and other COVID-19 variants. Finally, considering the important role of family physicians, who are the first points of contact with patient within the healthcare system, rapid identification and diagnosis of patients with different COVID-19 variants is important for proper management and to prevent any cardiac complications. Thus, this research was conducted to determine the diagnostic accuracy of sinus tachycardia as an independent indicator of COVID-19 and to compare our results between two different time points among different COVID-19 variants.

## Objectives

This study aimed to determine the diagnostic accuracy of sinus tachycardia as an independent indicator of COVID-19 and to compare our results between two different time points among different COVID-19 variants.

## Material and methods

### Study design

A cross-sectional analytical study was conducted to determine the diagnostic accuracy of sinus tachycardia as an independent indicator of COVID-19 and to compare our results to

compare our results between two different time points among different COVID-19 variants.

### Study participants

The study was conducted on 152 healthcare workers, either medical or paramedical, who fulfilled the inclusion criteria and were attending the the clinic was assigned for clinical consultation of health care worker who were employed in Prince Sultan Military Hospital, Taif.

### Setting

Recruitment took place at the clinic was assigned for clinical consultation of health care worker who were employed in Prince Sultan Military Hospital, Taif, at two different time points from 23/12/2021 to 13/1/2022 and from 15/5/2020 to 31/11/2020.

Al-Taif is located in the south-eastern part of the Western Province of Saudi Arabia, located at an elevation of 1,800 metres above sea level on the eastern slopes of the Al Sarawat Mountains, with a population of 1,083,693. Taif is 100 km from the city of Makkah, which is the most revered holy place of the international Muslim community, receiving more than 3 million visitors annually embracing the rituals of the Hajj pilgrimage.

### Inclusion criteria

All eligible adult patients ( $\geq 18$  years of age) of both gender with symptoms of suspected mild COVID-19 who were sent for home isolation or to a community quarantine facility without the need for admission within the specific duration whose medical data was fully documented were included. We selected cases with mild disease to avoid any significant confounders, such as cardiovascular complications of moderate or severe COVID-19 which may cause significant tachycardia and could interfered with our results.

### Exclusion criteria

Patients whose medical records were not fully documented or triaged, any admitted patient or patients who suffered from any comorbidities such as hyperthyroidism, any cardiac disease, anaemia or those taking any concomitant drugs having an effect on heart rate (i.e. beta-blockers, antiarrhythmic, ivabradine and/or digoxin) and which could interfere with our results were excluded from our sample.

## Sampling

### Sample size

To obtain a confidence interval (CI) of 95% and a 5% margin of error, a sample size of 156 participants was required.

### Sample technique

Convenience sampling was used to select equivalent numbers (78 electronic medical record) of patients from each of the two different time point from 23/12/2021 to 13/1/2022 and from 15/5/2020 to 31/11/2020.

Data was first collected from 23/12/2021 to 13/1/2022 by reviewing the electronic medical records of patients who attended the employee health clinic of the Family Medicine Department, Prince Sultan Hospital, Taif, with symptoms of suspected COVID-19. An equivalent number of the electronic medical records of patients from 15/5/2020 to 31/11/2020 were then reviewed retrospectively; however, the collection of our sample took much more time than expected (nearly 6 months) in comparison to the 1 month taken in the first step. This can be

explained due to the fact that in order to reach an equivalent number to our cases in first step, the duration of sample collection had to be extended to 6 months, as the incidence rate of the pandemic was low in contrast to the high incidence rate at the outbreak of the Omicron variant.

The electronic medical records were reviewed to collect data concerning age, gender, the onset date of COVID-19 symptoms and signs, days of symptoms at presentation, past medical history, systolic and diastolic Blood Pressures (BP), body temperature in degrees Celsius and laboratory exams at the time of attendance.

The patients included in our research were classified into 4 groups according to their COVID-19 result by Real Time PCR and the presence or absence of tachycardia as follows:

**Group A** – Those who had a negative result by RT COVID-19 PCR, and their pulse on attendance was  $\leq 100$  beats/minute.

**Group B** – Those who had a negative result by RT COVID-19 PCR, and their pulse on attendance was  $> 100$  beats/minute.

**Group C** – Those who had a positive result by RT COVID-19 PCR, and their pulse on attendance was  $\leq 100$  beats/minute.

**Group D** – Those who had a positive result by RT COVID-19 PCR, and their pulse on attendance was  $> 100$  beats/minute.

- In our sample, patients who had tachycardia  $> 100$  beats/minute associated with fever (oral temperature above  $37.8^{\circ}\text{C}$ ) either had COVID-19 or were not validated against the standardised-based evidence equation to determine if pulse was increased out of the proportion to fever or not [15, 16]. Patients with sinus tachycardia proportional to fever were excluded from the data which underwent analysis (4 patients total, 3 were excluded from the participants who were selected in 2020, and 1 patient was excluded from the participants who were selected in 2021). Statistical analysis was carried out on 152 participants.
- Any patients included in **group D** (those who had a positive result by RT COVID-19 PCR, and their pulse on attendance was  $> 100$  beats/minute) were routinely investigated after recovery (10 days after positive PCR result, as recommended by the COVID-19 management protocol in KSA) to exclude any cardiac complications for the following:
  - Pulse re-examination to confirm a baseline pulse.
  - ECG, to ensure that there was no abnormality in ECG after recovery nor any signs of pericarditis or myocarditis.
  - ESR and CRP, to exclude any possibility of active inflammatory processes.
  - CBC and TSH, to rule out other common causes of tachycardia such as anaemia or hyperthyroidism.

The sensitivity, specificity, ROC curve, negative predictive value and positive predictive value of sinus tachycardia were calculated for the patients who attended in late 2021 and early 2022, as well as the patients who attended in 2020, and both results were compared.

The result of 2020 is believed to be reflective of the accuracy of tachycardia as a clinical indicator of COVID-19 in predominant variants in Saudi Arabia at that duration, which is believed to be the SARS-COV-2 wild type, as the first variant of concern (Alpha variant) was designated on 14/12/2020 [19].

While the result of 2021–2022 is believed to be reflective of the accuracy of tachycardia as a clinical indicator of COVID-19 during the surge of cases after discovery of the first Omicron case on 1/12/2021 in Saudi Arabia [20].

## Outcome variables

Heart rate, the main outcome, was measured with a valid electronic device (pulse oximeter manufactured by the Riester company) for 1 minute and was expressed in beats per minute. Regularity of pulse was checked by radial artery palpation. Temperature was measured orally with a valid electronic device (welch Allyn) and was expressed in degree Celsius.

## Statistical analysis

Data analysis was carried out using IBM SPSS version 28. Descriptive characteristics were outlined as means, standard deviations (SD) or median, interquartile range (IQR) for continuous variables according to the sample distribution tested using the Shapiro-Wilk test, and the categorical variables were outlined as frequency and percentages. The association between pulse rate and COVID-19 was carried out using multiple logistic regression. An ROC curve was developed to obtain the appropriate cut off point, and a nomogram was created to help with prediction of the probability of COVID-19 using pulse rate.  $P < 0.05$  was considered statistically significant. Stata version 16 was used to develop the nomogram, and MedCalc version 20 was used for development of the ROC curve.

## Research ethics

All procedures performed in the study were in accordance with the ethical standards of the institutional research committee, as well as with the 1964 Helsinki Declaration and its later amendments. Ethical approval for the study was obtained from the Research Ethics Committee of Armed Forces Hospital (Code 2022-600). Confidentiality and anonymity were assured. Informed consent was obtained from all participants included in the study.

## Results

Our study included 152 electronic medical records of patients with symptoms of suspected mild COVID-19 with the mean age being  $35.47 \pm 7.09$  years. Out of the 152 patients, 50 were male (32.9%) and 102 were female (67.1%). After exclusion of patients with sinus tachycardia proportional to fever, 75 (49.3%) of the sample were selected from the electronic medical records of patients who attended the employee health clinic at the Family Medicine Department, Prince Sultan Hospital, Taif, from 15/5/2020 to 31/11/2020, while 77 (50.7%) of the samples were selected from 23/12/2021 to 13/1/2022. The mean pulse rate was  $94.52 \pm 16.01$  beats per minute. It was found that the prevalence of out of proportional sinus tachycardia among the participants diagnosed with COVID-19 in 2021 was triple that of the participants who were recruited in 2020 (61%, 26%, respectively). The mean temperature in our sample was  $36.99 \pm 0.58^{\circ}\text{C}$ . Among our participants, 51.3% were COVID-19 PCR positive, and the mean number of days of symptoms at presentation was  $2.01 \pm 1.29$  (Table 1).

Multiple logistic regression analysis was conducted to investigate the factors associated with COVID-19 among all the study samples, and it was found that there was significant association between pulse rate and COVID-19, with gender, age, temperature or days of symptoms having no effect. A higher pulse rate is associated with higher odds of having COVID-19 (OR = 1.04, 95% CI: 1.02–1.07,  $p = 0.001$ ) (Table 2).

Table 3 shows the results of multiple logistic regression analysis, which studied the association between pulse rate and COVID-19 among each group. It was observed that there was no significant association between pulse rate and COVID-19 among the participants who were recruited in 2020, while there was a significant association between pulse rate and COVID-19 among the participants who were recruited in 2021–2022, with gender, age, temperature or days of symptoms having no effect. A higher pulse rate is associated with higher odds of having COVID-19 (OR = 1.09, 95% CI: 1.04–1.14,  $p < 0.001$ ).

Nomogram analysis was conducted to investigate whether pulse rate is a predictor for the probability of having COVID-19, and it was found that there was direct relationship between pulse rate and the probability of having COVID-19 among all the study samples (Figure 1).

**Table 1. Personal and clinical characteristics of the study samples (n = 152)**

Gender	male n (%)	50	32.9
	female n (%)	102	67.1
Age	mean, SD	35.47	7.09
Group	2020 n (%)	78	50
	2021–2022 n (%)	78	50
Pulse rate	mean, SD	94.52	16.01
Prevalence of out of proportional sinus tachycardia in all study samples (152)	2020 n (%)	20	26
	2021–2022 n (%)	31	41
Prevalence of out of proportional sinus tachycardia in COVID-19 positive patients	2020 n (%)	10	26
	2021–2022 n (%)	25	61
Temperature	mean, SD	36.99	0.58
Days of symptoms at presentation	mean, SD	2.01	1.29
COVID-19 PCR result among all study samples (152)	(2020) n = 75 negative n (%) positive n (%)	36	48
		39	50
	(2021) n = 77 negative n (%) positive n (%)	36	46
		41	53

**Table 2. Multiple logistic regression for the association between pulse rate and COVID infection among all study samples (n = 152) controlling for other variables**

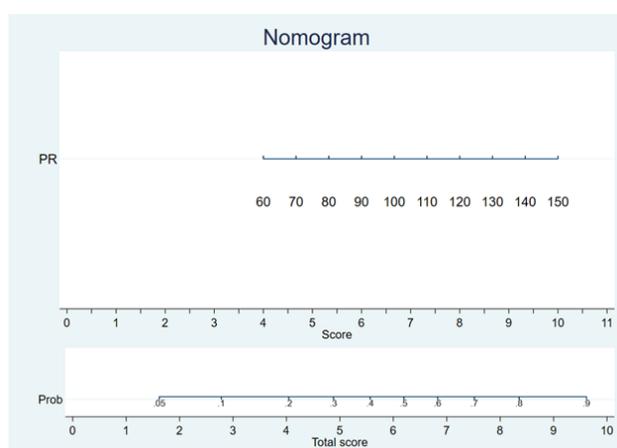
	Unadjusted OR	Adjusted OR	95% CI of OR		p
Gender (female)	1.08	0.97	0.47	1.99	0.938
Age	1.00	1.00	0.96	1.05	0.851
Temperature	1.28	0.89	0.47	1.66	0.705
Days of symptoms at presentation	0.86	0.92	0.70	1.20	0.518
Pulse rate	1.04	1.04	1.02	1.07	0.001

\*Statistically significant at p < 0.05.

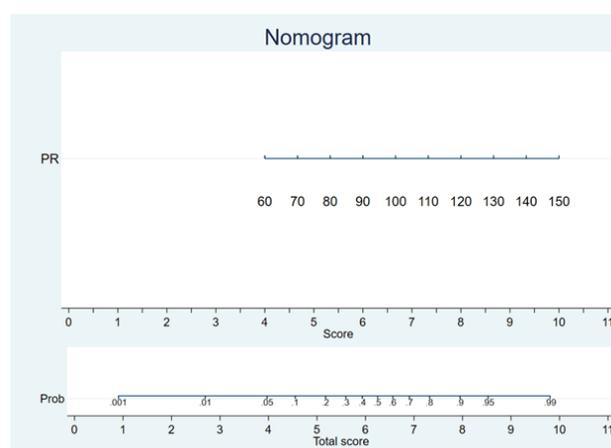
**Table 3. Multiple logistic regression for the association between PR and COVID infection for each group**

	2020 (n = 75)			2021–2022 (n = 77)		
	OR	(95% CI)	p	OR	(95% CI)	p
Gender (female)	0.74	0.28–1.92	0.534	1.73	0.49–6.08	0.396
Age	1.05	0.98–1.13	0.190	1.00	0.92–1.08	0.988
Temperature	0.87	0.40–1.87	0.715	0.76	0.22–2.60	0.660
Days of symptoms at presentation	0.93	0.620–1.39	0.714	0.95	0.63–1.42	0.791
Pulse rate	0.99	0.96–1.03	0.752	1.09	1.04–1.14	< .001

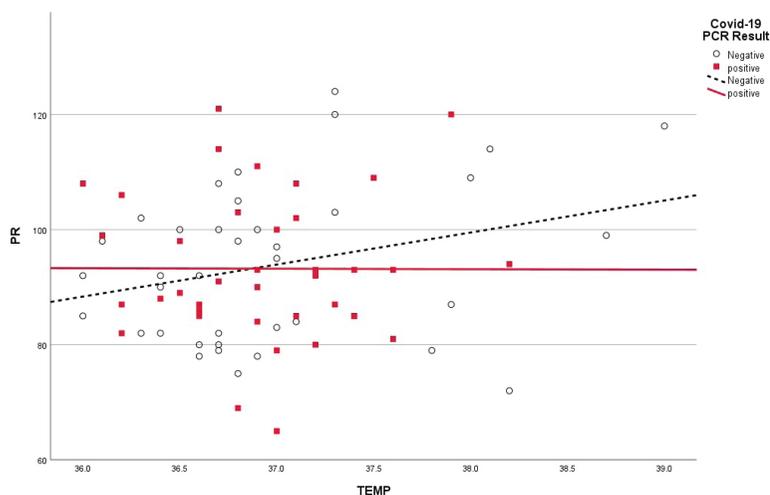
\*Statistically significant as p < 0.05.



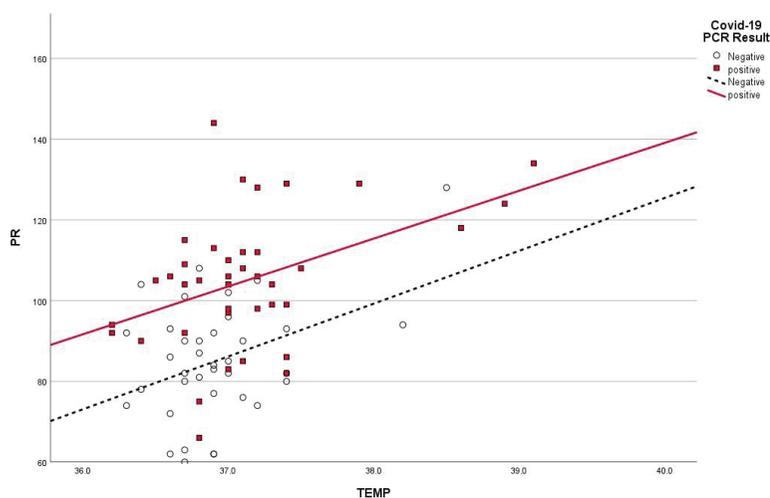
**Figure 1.** Nomogram for pulse rate as a predictor for the probability of having of having COVID-19 infection among all the study samples (n = 152)



**Figure 2.** Nomogram for pulse rate as a predictor for the probability of having COVID-19 infection among the study samples who were recruited in 2021–2022 (n = 77)



**Figure 3.** Scatter plot for the association between pulse rate and temperature segregated by COVID-19 infection status among the study samples who were recruited in 2020 ( $n = 75$ )



**Figure 4.** Scatter plot for the association between PR and temperature segregated by COVID-19 infection status among the study samples who were recruited in 2021–2022 ( $n = 77$ )

Figure 2 clarifies that the probability of having COVID-19 was increased by increasing pulse rate.

Figure 3 showed the results of a scatter plot analysis studying the association between pulse rate and temperature segregated by COVID-19 status among participants who were recruited in 2020, and it was observed that there was positive association between pulse rate and temperature for negative COVID-19 cases only. On the other hand, the association between pulse rate and temperature segregated by COVID-19 status among participants who were recruited in 2021 is presented in Figure 4, which shows a positive relationship between pulse rate and temperature for both positive and negative COVID-19 cases. However, the fit line for positive cases is higher than that for negative cases (higher intercept). This means that positive COVID-19 cases have higher pulse rates when compared to the negative COVID-19 cases.

Finally, the results of the Area under the ROC curve (AUC) analysis are summarised in Table 4, and it was found that there was statistically significant association between pulse rate and having COVID-19 among the participants who were recruited in 2021 ( $p < 0.001$ ).

Table 5 shows the diagnostic accuracy of sinus tachycardia as an independent indicator of COVID-19 based on the Youden index among participants who were recruited in 2021, and it was found that sinus tachycardia had high sensitivity, specificity, positive and a negative predictive value (75%, 84%, 83%, 76%, respectively).

	All data	2020	2021–2022
Area under the ROC curve (AUC)	0.683	0.509	0.834
95% Confidence interval	0.603 to 0.756	0.390 to 0.626	0.732 to 0.909
$p$	< 0.001	0.901	< 0.001

	value	95% CI
Cut off point	> 96	
Sensitivity	75.00	58.8–87.3
Specificity	83.78	68.0–93.8
Positive predictive value	83.3	70.2–91.4
Negative predictive value	75.6	64.0–84.4

## Discussion

The present study was conducted to determine the diagnostic accuracy of sinus tachycardia as an independent indicator of COVID-19 and to compare our results between two different time points among different COVID-19 variants. Among the 152 electronic medical records of patients with symptoms of suspected mild COVID-19 who were enrolled in the current study, 50 were male (32.9%), and 102 were female (67.1%), with the mean age

being  $35.47 \pm 7.09$  years. The mean pulse rate among our recruited sample was  $94.52 \pm 16.01$  beats per minute, and the mean temperature was  $36.99 \pm 0.58^\circ\text{C}$ . Among our participants, 51.3% were COVID-19 PCR positive, with the mean number of days of symptoms at presentation being  $2.01 \pm 1.29$ .

In the current study, it was found that the prevalence of out of proportional sinus tachycardia among the participants diagnosed with COVID-19 in 2021 was triple that of the participants who were recruited in 2020 (61%, 26%, respectively). As previously mentioned, the result from 2020 is believed to be reflective of the accuracy of tachycardia as a clinical indicator of COVID-19 for predominant variants in Saudi Arabia at that time, which is believed to be the SARS-CoV-2 wild type, as the first variant of concern (Alpha variant) was designated on 14/12/2020 [19], while the result of 2021–2022 is believed to be reflective of the accuracy of tachycardia as a clinical indicator of COVID-19 during the surge of cases after the discovery of first Omicron case on 1/12/2021 in Saudi Arabia [20].

Our results were consistent with the findings of Jia He et al., who conducted a case report to study characteristic electrocardiographic manifestations in patients with COVID-19 and who reported that sinus tachycardia is the most common ECG finding in COVID-19 patients [21].

Our findings were in agreement with the results of a prospective observational study conducted by Jae Hyung Cho et al. in the western United States to investigate cardiac arrhythmias in hospitalised patients with COVID-19, and they declared that sinus tachycardia was the most common arrhythmia detected in 39.9% (57 out of 143) of their patients [22].

In the present research, multiple logistic regression analysis was conducted to investigate factors associated with COVID-19 among the entire study sample, and it was found that there was significant association between pulse rate and COVID-19, with gender, age, temperature or days of symptoms having no effect. A higher pulse rate is associated with higher odds of having COVID-19 (OR = 1.04, 95% CI: 1.02–1.07,  $p = 0.001$ ).

These findings were compatible with the findings that were published concerning stealth Omicron symptoms on 15 March 2022 and which found that a higher pulse rate is associated with

a higher probability of having COVID-19, especially the Omicron variant [23].

Furthermore, our findings were consistent with the results of a study that was conducted by Trevano et al., who found that heart rate is a simple and quick way to evaluate sympathetic activity. Although some concern remains on its capacity to discern between different components of the autonomic nervous system, it can be used for a first screening [24].

On the other hand, our findings were inconsistent with the findings of a study that was conducted by Alessandro Maloberti et al., who assessed the prevalence of elevated heart rate upon discharge in patients hospitalised for COVID-19, and they declared that a high heart rate at discharge ( $> 100$  bpm, i.e. sinus tachycardia) in COVID-19 patients is not such a frequent problem, as it only involved 5.5% of their population. On the other hand, they reported that the presence of sinus tachycardia seemed to be strongly related to evidence of a severe course of disease [25].

At the best of our knowledge, our research to study the diagnostic accuracy of sinus tachycardia as an independent indicator of COVID-19 disease, especially the Omicron variants, is novel and no paper has been published regarding this topic yet.

### Limitations of the study

There may be some possible limitations in this study. For example, the small sample size and sampling bias, where the selected participants may not represent the real population under study, may affect the generalisation of the results. Additionally, no long-term data regarding heart rate following discharge is available, and thus we cannot answer the question regarding how long this problem persists over time in patients suffering from out of proportional sinus tachycardia.

### Conclusions

The study highlights the diagnostic accuracy of sinus tachycardia as an independent indicator of COVID-19, especially the Omicron variant. It was found that a higher pulse rate is associated with higher odds of having COVID-19.

Source of funding: This work was funded from the authors' own resources.

Conflicts of interest: The authors declare no conflicts of interest.

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Received: 19.09.2022

Reviewed: 11.10.2022

Accepted: 16.11.2022

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