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ORIGINAL ARTICLE

Clinical Outcomes of Direct-Acting Oral Anticoagulants in COVID-19 Patients with Cardiometabolic Comorbidities at a Tertiary Care Hospital

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ABSTRACT

OBJECTIVE: To evaluate the thrombotic and hemorrhagic outcomes with DOACs in COVID-19 patients with Cardiometabolic diseases that can help in future to treat COVID patients and combat the pandemic.

METHODOLOGY: A descriptive study was conducted among COVID-19 patients in the COVID-19 Isolation Wards and the ICU of Nishtar Medical University, Multan, Pakistan, from January to June 2022. A total of 121 patients who met the inclusion criteria were enrolled in the study. All the patients were put on DOAC therapy, either Rivaroxaban, Apixaban, Edoxaban or Dabigatran. They were followed up for up to 30 days after COVID-19 diagnosis to see for the development or absence of thrombotic or hemorrhagic events. Data were analyzed using SPSS 23.

RESULTS: Mean age of the participants was 60.0 ± 10.7 years. Over a period of 30-day follow-up with DOACs, 38.9% patients developed hemorrhage and 28.9% developed thrombosis. Frequency of thrombosis was significantly higher in males compared to females (36.9% vs. 19.6%; p-value 0.037), and higher in obese compared to non-obese (42.1% vs. 22.9%, p-value 0.031). The frequency of thrombosis differed significantly among DOACs, with the highest rate in Dabigatran (50%) and the lowest in Rivaroxaban (17.4%).

CONCLUSION: Our study found that haemorrhage occurred in 38.9% of patients on DOACs, and thrombosis was lowest (17.4%) in patients on Rivaroxaban compared to other DOACs. Therefore, Rivaroxaban is associated with a lower frequency of thrombosis.

KEYWORDS: COVID-19, Cardiometabolic, Anticoagulants, Obesity, Thromboembolism

INTRODUCTION

SARS-CoV-2, a recently discovered novel coronavirus that causes a lethal and contagious disease, was named Coronavirus (COVID-19) and declared a pandemic by the World Health Organization (WHO) on March 11, 2020. Cardiometabolic disease is most prevalent in COVID-19 patients and linked to worse COVID-19 outcomes, such as death, mechanical ventilation, and intensive care, as well as higher susceptibility to the coronavirus[2]. Cardiometabolic disease refers to a group of metabolic abnormalities (such as poor lifestyles, poor diets, obesity, pathological changes like insulin resistance, hyperglycemia, dyslipidemia, abdominal obesity, and hypertension) that increase the risk of cardiovascular diseases and type 2 diabetes[2]. Thrombotic events are common and often fatal in patients with COVID-19, particularly among those with pre-existing cardiometabolic diseases and cardiovascular disease[3-4]. According to a previous study, the prevalence of thrombotic complications stands at 43%, while haemorrhagic complications occur in 8% of cases in COVID-19 patients[4]. Haemorrhage is bleeding from a damaged or ruptured blood vessel, while thrombosis is the formation of blood clots[4]. Thrombotic events are associated with considerable mortality and morbidity because of high ferritin levels, complement dysfunctions, and macrophage activation[5]. COVID-19 induces a hypercoagulable state driven by endothelial dysfunction and a systemic inflammatory response. This cooperation significantly increases the risk of arterial and venous thrombosis[6,] with a particularly high prevalence of thromboembolic complications among critically ill patients[7].

Anticoagulants have a significant role in the treatment of cardiovascular and thromboembolic diseases[8]. The common anticoagulants warfarin (vitamin K antagonists) and direct-acting oral anticoagulants (DOACs) are recommended treatments for thrombosis, and their role in thromboprophylaxis of cardiometabolic diseases has also been well established[8]. DOACs in COVID-19 patients significantly increase hemorrhage risk due to severe drug-drug interactions and virus-induced physiological changes[4]. However, their efficacy in preventing stroke and systemic embolism, combined with lower rates of intracranial haemorrhage, gives them a superior safety profile compared with traditional Vitamin K antagonists[8]. Further, DOACs do not require regular laboratory monitoring as compared to warfarin and are not affected by food or alcohol[8]. DOACs consist of a factor IIa inhibitor, such as Dabigatran, and three factor Xa inhibitors, such as Rivaroxaban, Apixaban, and edoxaban[8]. Similar to Dabigatran, Factor Xa inhibitors rivaroxaban, Apixaban, and Edoxaban have been linked to successful treatment and prevention of recurrent venous thromboembolism (VTE)[9,10] as well as a decreased incidence of significant haemorrhage[11].

DOACs are generally preferred over traditional anticoagulants, but there is a critical lack of head-to-head evidence identifying which specific treatment (Apixaban, Rivaroxaban, edoxaban, or Dabigatran) optimizes the balance for the high-risk phenotype. There is a lack of local data on DOAC-associated outcomes in COVID-19 patients with cardiometabolic diseases.

This study aims to describe thrombotic and hemorrhagic outcomes with different DOACs in hospitalized COVID-19 patients with cardiometabolic diseases, and to identify the best DOAC treatment among different types to help in the future treatment of COVID-19 patients, combat the viral pandemic, and generate local observational data on DOAC-associated outcomes in COVID-19 patients with cardiometabolic diseases. Therefore, we conducted a prospective observational study of hospitalized COVID-19 patients receiving DOAC therapy to systematically document clinical outcomes over 30 days.

METHODOLOGY

Study design

A descriptive study was conducted among 121 COVID-19 patients from January to June 2022 in the COVID Isolation Wards and the ICU of Nishtar Medical University, Multan, Pakistan, using a non-probability, consecutive sampling technique. Informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Sample size

The sample size of 121 was calculated using the WHO software using the formula for a single proportion[9]. Frequency of thrombotic events (both arterial and venous thrombosis) = 8.5%, Confidence level = 95%, Margin of error= 05%.

Inclusion and exclusion criteria

Patients of both genders, males and females, between the age group of 35-80 years, suffering from one or more cardiometabolic diseases (diabetes, hypertension or obesity), and COVID-19 confirmed patients tested with PCR were included in the study, specifically those not on anticoagulation therapy. Leukaemia/lymphoma patients in the second and third trimesters of pregnancy were also included in this study, as DOACs are safe to use. At the same time, pregnant ladies in the first trimester were excluded, as DOACs are not approved by the FDA to be given to pregnant ladies in the first trimester. Patients who fail to follow up after 30 days, those who died within 7 days of admission in COVID isolation or ICU ward, individuals with inherited bleeding or thrombophilia disorders, non-compliant patients refusing DOACs, and those with a prior history of DVT or thrombosis were also excluded from this study.

Data collection procedure

After obtaining ethical review committee approval (No. 4120; Dated 09-03-2022), the PCR-positive COVID-19 patients admitted to the COVID isolation ward and ICU of Nishtar hospital with cardiometabolic diseases (as per the patient's previous medical records) were included in the study. Detailed history and general physical examination were performed via non-probability sampling and documented on a specially designed pro forma. Clinical outcomes were assessed according to standardized symptomatic presentations. Thrombotic events were identified by signs of deep vein thrombosis (DVT), such as localized pain, swelling, warmth, and redness in the limbs, or by pulmonary embolism (PE), characterized by chest pain and dyspnea. Arterial thrombosis was defined by neurological deficits (sudden confusion, speech difficulties, hemiparesis, or severe headache) or cardiac distress (intense chest pain, dizziness, and respiratory distress). A brain haemorrhage was identified through sudden severe headache, vision changes, or loss of consciousness. Internal hemorrhage (abdominal/organ-specific) was noted via abdominal swelling, pain, fatigue, and hematemesis or melena. Chest hemorrhage (hemothorax) was marked by coughing up blood and chest pain, and musculoskeletal hemorrhage was recorded in cases of severe bruising and joint-specific swelling and pain. Participants were administered DOAC therapy for COVID-19 management, according to standard clinical protocols, with the specific agent and dosage determined at the treating physician's discretion. The therapeutic regimens included: Rivaroxaban (15 mg BID), Apixaban (initiated at 10 mg BID for the first 7 days, followed by a maintenance dose of 5 mg BID), Edoxaban (60 mg QD), or Dabigatran (150 mg BID). All medications were administered orally. Patients were monitored for 30 days post-COVID-19 diagnosis to assess the occurrence or absence of thrombotic and hemorrhagic complications. Diagnostic

verification of suspected events was conducted using specialized imaging modalities: color Doppler ultrasound for DVT, computed tomography pulmonary angiography (CTPA) for pulmonary embolism, and angiography for acute myocardial infarction, cerebral infarction, and cerebral venous thrombosis. All diagnostic procedures were performed at the Radiology Department of Nishtar Hospital, Multan, Pakistan where these advanced facilities are fully operational. Essential medications were provided to patients free of cost through the Nishtar Hospital Outpatient Department (OPD) as part of the public healthcare initiative, and the primary investigators personally funded all remaining investigative costs.

Data analysis

Data were analyzed on SPSS version 23.0. Descriptive statistics were employed to summarize the data. Continuous variables (such as age and BMI) were expressed as mean ± standard deviation (SD). In contrast, categorical variables (such as gender, age groups, residential status, diabetes mellitus, hypertension, obesity, and clinical outcomes) were expressed as absolute frequencies and percentages. To address potential confounding, stratification was performed for effect modifiers, including gender, age, residential status, and comorbidities (diabetes, hypertension, and obesity). The Chi-square test was subsequently applied to these stratified groups to evaluate the association between these variables and the thrombotic/hemorrhagic outcomes of DOAC therapy. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

The mean age of the participants was 60.0 ± 10.7 years. There were 53.7% (n=65) males and 46.3% (n=56) female participants. Mean body mass index (kg/m^2) of the patients was 26.6 ± 2.3. 47.9% (n=58) of patients came from rural areas and 52.1% (n=63) from urban areas. There were 31.4% (n=38) obese, 55.4% (n=67) diabetics and 66.9% (n=81) hypertensives in the study group **(Table I).**

Table I: Characteristics of COVID-19 patients with cardiometabolic conditions (N=121)

Factors	Categories	Statistical values	Results
Age (Years)	-------	mean ± SD	60.0 ± 10.7
Body mass index (kg/meter^2)	-------	mean ± SD	26.6 ± 2.3
Gender	Male	n (%)	65 (53.7)
	Female	n (%)	56 (46.3)
Obesity	Yes	n (%)	38 (31.4)
	No	n (%)	83 (68.6)
Area of residence	Rural	n (%)	58 (47.9)
	Urban	n (%)	63 (52.1)
Diabetes Mellitus	Yes	n (%)	67 (55.4)
	No	n (%)	54 (44.6)
Hypertension	Yes	n (%)	81 (66.9)
	No	n (%)	40 (33.1)

**SD=standard deviation, n=Number of patients, %=percentage*

Most commonly prescribed directly acting oral anticoagulants (DOACs) were Rivaroxaban in 38% (n=46), followed by Apixaban in 33.9% (n=41), Edoxaban in 19.8% (n=24) and Dabigatran in 8.3% (n=10) **(Figure IA).** Over a 30-day follow-up period, 38.9% (n=47) developed haemorrhage (bleeding risk), and 28.9% (n=35) developed thrombosis (blood clotting risk) **(Figure IB).**

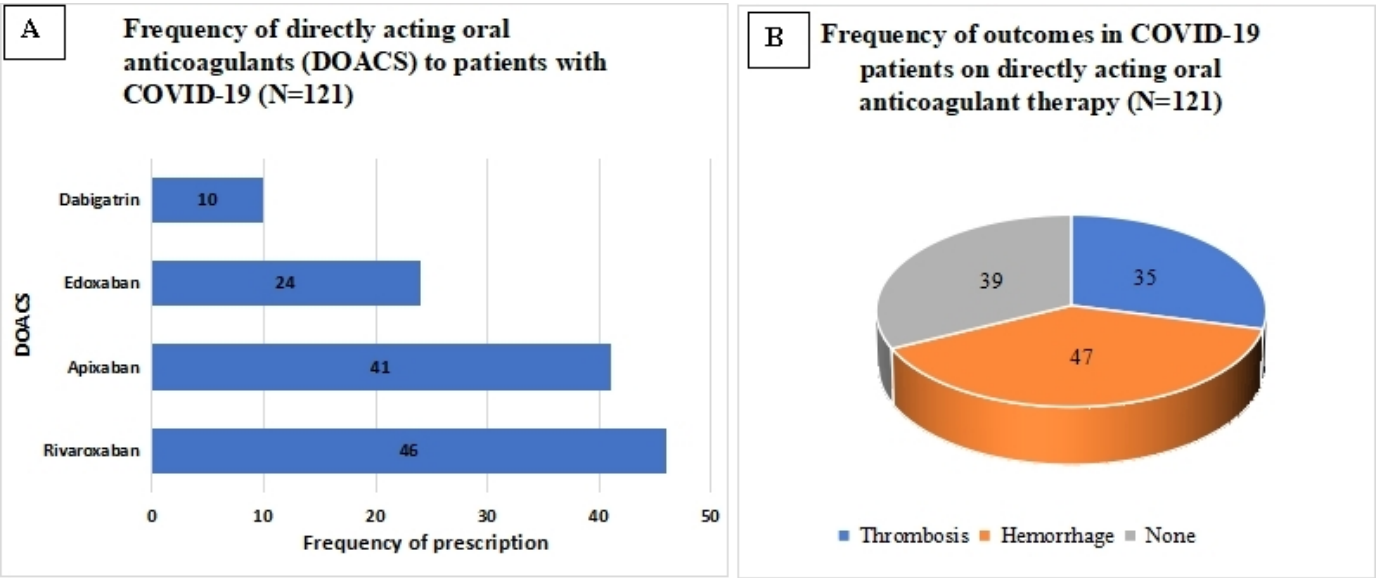

Figure I: Frequency of directly acting oral anticoagulants (DOACs) to patients with COVID-19 (A) and frequency of outcomes in COVID-19 patients on directly acting oral anticoagulant therapy (B).

Frequency of thrombosis was significantly higher in males compared to females (36.9% vs. 19.6%; p-value 0.037), higher in obese compared to non-obese (42.1% vs. 22.9%; p-value 0.031) and higher in patients from rural areas compared to urban areas (37.9% vs. 20.6%; p-value 0.036). However, age, diabetes mellitus and hypertension did not significantly affect the occurrence of thrombosis **(Table II).** The frequency of thrombosis differed significantly among DOACs, with Dabigatran (50%), Edoxaban (45.8%), and Rivaroxaban (17.4%) in descending order **(Table III).** Age, gender, area of residence, obesity, diabetes mellitus and hypertension did not significantly affect the frequency of Hemorrhage in COVID-19 patients on DOACs **(Table IV).**

Table II: Effect of age, gender, area of residence, obesity, diabetes mellitus and hypertension on frequency of Thrombosis in COVID-19 patients on DOACs (N=121)

Factors		Thrombosis		p-value*
		Yes	No	
Age Groups	Up to 60-years	20 (34.5)	38 (65.5)	0.196
	> 60-years	15 (23.8)	48 (76.2)	
Gender	Male	24 (36.9)	41 (63.1)	0.037
	Female	11 (19.6)	45 (80.4)	
Obesity	Yes	16 (42.1)	22 (57.9)	0.031
	No	19 (22.9)	64 (77.1)	
Area of residence	Rural	22 (37.9)	36 (62.1)	0.036
	Urban	13 (20.6)	50 (79.4)	
Diabetes Mellitus	Yes	21 (31.3)	46 (68.7)	0.514
	No	14 (25.9)	40 (74.1)	
Hypertension	Yes	24 (29.6)	57 (70.4)	0.808
	No	11 (27.5)	29 (72.5)	

**Chi-square test*

Table III: Frequency of thrombosis among different DOACs in COVID-19 patients (N=121)

Type of DOACs	Thrombosis		p-value*
	Yes	No	
Rivaroxaban	8 (17.4%)	38 (82.6%)	0.036
Apixaban	11 (26.8%)	30 (73.2%)	
Edoxaban	11 (45.8%)	13 (54.2%)	
Dabigatran	5 (50.0%)	5 (50.0%)	

**Chi-square test*

Table IV: Effect of age, gender, area of residence, obesity, diabetes mellitus and hypertension on frequency of Hemorrhage in COVID-19 patients on DOACs (N=121)

Factors		Hemorrhage		p-value*
		Yes	No	
Age Groups	Up to 60-years	27 (46.6)	31 (53.4)	0.095
	> 60-years	20 (31.7)	43 (68.3)	
Gender	Male	24 (36.9)	41 (63.1)	0.641
	Female	23 (41.1)	33 (58.9)	
Obesity	Yes	18 (47.4)	20 (52.6)	0.193
	No	29 (34.9)	54 (65.1)	
Area of residence	Rural	21 (36.2)	37 (63.6)	0.568
	Urban	26 (41.3)	37 (58.7)	
Diabetes Mellitus	Yes	24 (35.8)	43 (64.2)	0.447
	No	23 (42.6)	31 (57.4)	
Hypertension	Yes	27 (33.3)	54 (66.7)	0.077
	No	20 (50)	20 (50)	

**Chi-square test*

DISCUSSION

The study was conducted among COVID-19 patients with cardiometabolic diseases who were treated with direct-acting oral anticoagulants (DOACs). Thrombosis is one of the most common and well-known complications of COVID-19[3,4]. The use of DOACs may lead to more convenient and safe antithrombotic therapies with increased patient compliance compared to vitamin K antagonists[8]. Therefore, in this study, the frequency of thrombosis with DOACs in COVID-19 patients with cardiometabolic diseases was studied, and three factor Xa inhibitors (Rivaroxaban, Apixaban, and edoxaban) and a newly developed direct thrombin inhibitor (Dabigatran) were used to determine their effectiveness against thrombosis.

Previous studies reported that cardiometabolic multimorbidity is highly prevalent among COVID-19 patients and is independently associated with an increased risk of hospitalization and poorer clinical outcomes[12-13] which is consistent with our findings, as 121 COVID-19 patients in our study are diagnosed with cardiometabolic diseases.

In our study, the mean age of COVID-19 patients with cardiometabolic diseases was 60 years, which is somewhat consistent with **Piraee et al.** [14], who found a mean age of 60 years in COVID-19 patients with cardiovascular diseases. **Chen et al.** [15] reported that the median age of 56 years in COVID-19 patients with cardiometabolic diseases. These studies show that the age of COVID-19 patients with cardiometabolic diseases is approximately 55 to 60 years.

Cohen et al. found that the COVID-19 death rate for men was 29.9% greater than for women[16,] which is consistent with our study, whereas the frequency of COVID-19 patients was significantly higher in males compared to females. Previous studies similarly show a higher prevalence of COVID-19 among males than among females[14,15].

The results of the study found that the COVID-19 patients with cardiometabolic diseases were more common in non-obese (68.6%) compared to obese (31%) patients. At the same time, **Hendren et al.** [17] reported that body mass index (BMI) affects the morbidity and mortality in patients with COVID-19 and found obese patients face higher hospitalization rates and risks of death or ventilation from COVID-19, which is consistent with our study, which may be due to the small sample size of our study. The sample size was initially based on an anticipated 8.5% thrombotic event frequency; the observed rate was substantially higher. This discrepancy likely reflects the elevated risk profile and high burden of cardiometabolic multimorbidity in our cohort. While this higher event rate increases the study's statistical power to detect treatment effects, it also highlights a previously underestimated prothrombotic intensity in this population compared to earlier estimates. Further, our investigations found that hypertension and diabetes mellitus were most common among COVID-19 patients with cardiometabolic diseases, consistent with previous studies showing a high prevalence of hypertension and diabetes mellitus in COVID-19 patients with cardiometabolic diseases[15,18].

However, age, diabetes mellitus and hypertension with DOACs did not significantly affect the occurrence of thrombosis and hemorrhage in our study. **Cohen et al.** [16] reported a 35.8% higher rate of thrombotic diagnosis in men than in women, consistent with our study. In contrast, we find more thrombosis in males than in females. Wilcox et al. also found that 34% of hospitalizations resulted in mortality or thrombosis, and that men were more likely to have these events (36% vs 29% in women, $p < 0.001$)[19]. Sattar et al. reported that obesity has negative impacts on lung function, reducing forced expiratory volume and forced vital capacity, in addition to cardiometabolic and thrombotic implications[20]. **Sattar et al.** [20] reported that higher relative fat mass is associated with adverse health effects and COVID-19 critical illness,

especially in Asians, who may have lower fitness and more fat at lower BMI. Wang et al. reported that individuals with class I and III obesity had significantly increased risk-adjusted probabilities of venous thromboembolism (VTE) compared to patients without obesity[21]. Still, our study shows that thrombosis was not common in obese patients compared to non-obese patients, which may be because our patients were treated with DOACs. **Magro et al.** [22] reported that widespread cytokine activation may trigger thrombosis in COVID-19, activating platelets and the complement system. The risk of arterial and venous thrombosis is known to be increased by COVID-19, leading to a focus on thrombo-inflammation and antithrombotic therapy, especially anticoagulant therapy[23].

Rivera-Caravaca et al. [24] reported that patients receiving vitamin K antagonists before the diagnosis of COVID-19 demonstrated a 43% greater risk of thrombotic events and ischemic stroke within 30 days than those on DOACs, with comorbidities being taken into account using propensity score matching. Rivaroxaban was found to be more effective in preventing thromboembolism in a study from Brazil[25] which is consistent with our study. The results of our study found that the frequency of thrombosis differed significantly among different DOACs, being highest in Dabigatran (50%), followed by edoxaban (45.8%). It was lowest for Rivaroxaban (17.4%), indicating the effectiveness of Rivaroxaban, but the sample size of Dabigatran was very small, which may affect the generalizability of these findings. Previous studies also show the effectiveness of Rivaroxaban. Ramacciotti et al. found that high-risk patients hospitalized with COVID-19 who were given Rivaroxaban 10 mg daily for 35 days post-discharge had a significantly lower rate of venous thromboembolism (VTE) and related mortality (3% vs 9%; p = .0293) [25]. This suggests the prothrombotic state of COVID-19, supporting post-discharge anticoagulation in certain high-risk patients. Similarly, **Weitz et al.** [26] found that Rivaroxaban is an effective treatment for thromboembolism. They compared the effectiveness of Rivaroxaban and aspirin and found that Rivaroxaban was a more effective treatment than aspirin and was associated with bleeding.

However, there are discrepancies in the published data for DOACs in the COVID-19 field. Many COVID-19 patients who had been receiving DOAC therapy were shifted to heparins during hospitalization because it is anticipated that they will take drugs that interfere with DOACs or because they have coagulation system and homeostasis issues[27]. The discrepancies in published data may have been the result of several factors, such as study populations, study designs, and the timing of the studies during the evolving pandemic. In addition to these, many antiviral and immunosuppressant medications used to treat COVID-19 have significant interactions with DOACs, making their dosing (drug-drug interactions) and effects unpredictable.

To summarize, the frequency of thrombosis in COVID-19 patients and the superior efficacy of Rivaroxaban compared to other DOACs in this patient population were examined. These findings are significant, particularly given existing data discrepancies in the field, and suggest that specific patient characteristics or underlying conditions may influence individual DOAC performance, which can help in the future to control COVID patients and the viral pandemic.

Limitation: A primary limitation of this study is that DOAC selection was determined by physician preference rather than randomization, introducing uncontrolled confounding by indication that may have influenced the observed clinical outcomes. Additionally, the limited sample size and observational study design may limit the generalizability of these findings to broader, more diverse patient populations.

CONCLUSION

Our study concludes that over a period of 30-day follow-up, COVID-19 patients with cardiometabolic diseases on DOACs developed 38.9% hemorrhage and 28.9% thrombosis. Male patients were at a higher risk of developing thrombosis. The frequency of thrombosis was lowest (17.4%) in patients on Rivaroxaban. So, Rivaroxaban is relatively more effective than other DOACs such as Apixaban, Edoxaban, and Dabigatran.

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Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION

Fatima S: Conception and design of the study, data collection and interpretation, writing – original draft and finalized the manuscript.
Kaleemi S: Coordinated laboratory testing, contributed to the literature review and methodology section.
Huda NU: Formal analysis and drafted the results section of the manuscript.
Hafeez F: Assisted in patient recruitment, data entry, and reviewed the manuscript for accuracy.
Akhtar A: Helped in conducting the experiment and manuscript writing – review & editing.
Khan S: Critical review of manuscript and help in reference correction.

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