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PHARMACOEPIDEMIOLOGY

A historical cohort study to investigation of statins safety in COVID-19 hospitalized patients

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Summary
Background and objectives. — A notable proportion of COVID-19 patients need statins for their co-existing conditions. Statins possess several anti-inflammatory properties. We have attempted to describe potential association of exposure to statins and severity of COVID symtpoms in a historical study in hospitalized COVID-19 patients.
Methods. — This single-center, historical cohort study was performed in Baharloo hospital as a referral hospital for COVID-19 patients in Tehran. Patients were divided into two groups; 163 statins users and 547 non-users. Mortality rate, intensive care unit (ICU) admission and length of hospitalization were compared between studied groups. In addition, during the investigation, pre-existing conditions were evaluated for groups. If a significant difference was observed between groups, the feature was considered in the adjustment of the odds ratio.

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Results. — At the beginning, statistical analysis study showed that statins users had significantly ($p < 0.0001$) higher mortality rate, ICU admission and length of hospitalization. But after implementation of variables such as age, sex, diabetes, hypertension status, stroke, dyslipidemia, cardiovascular diseases, chronic kidney disease (CKD), corticosteroids, renin-angiotensin-aldosterone axis inhibitors and proton pump inhibitors (PPIs) for adjustment of the odds ratio, a considerable alteration appeared in the studied values. Following adjustment of odds ratio it was shown that statins did not change mortality (95% CI, OR 0.71 (0.41—1.22), $p = 0.22$), ICU admission (95% CI, OR 1.05 (0.66—1.66), $p = 0.835$) and length of hospitalization (95% CI, OR 1.30 (0.78—2.17), $p = 0.311$). In addition, we found that statins could not decrease inflammatory markers in COVID-19 infected patients.
Conclusion. — The use of statins did not seem to change outcomes in COVID19.

Abbreviations

ACE2	angiotensin-converting enzyme 2
AKI	acute kidney injury
BMI	body mass index
COPD	chronic obstructive pulmonary disease
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
CT	computed tomography
ECMO	extracorporeal membrane oxygenation
FDA	Food and Drug Administration
ICU	intensive care unit
IL6	interleukin 6
INF β	interferon-β
IVIG	intravenous immunoglobulin
LDH	lactate dehydrogenase
MYD88	myeloid differentiation primary response 88
NF-κB	nuclear factor kappa B
NIV	non-invasive ventilation
PCR	polymerase chain reaction
PPIs	proton pump inhibitors
RA	rheumatoid arthritis
RSV	respiratory syncytial virus
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SLE	systemic lupus erythematosus
TLR	toll-like receptor
TUMS	Tehran University of Medical Sciences

Introduction

Since the beginning of the coronavirus disease 2019 (COVID-19) outbreak, a significant number of patients have lost their lives every day [1]. Inflammation associated by COVID-19 leads to multi-organ damage and is responsible for a great proportion of disease burden [2,3]. So far, several studies attempted to clarify the effects of previously Food and Drug Administration (FDA)-approved medications such as hydroxychloroquine, corticosteroids and remdesivir on this viral infection and its outcomes. Hence, repurposing previously approved drugs is an easier, cost-effective and swift solution to solve problems such as COVID-19 [4,5]. Previous studies revealed that statins possess anti-inflammatory, anti-oxidant, immunomodulatory and anti-thrombotic properties. Further, they can contribute to the upregulation of angiotensin-converting enzyme 2 (ACE2), preventing the deleterious effects of angiotensin II on the lungs [6,7].

Statins can modify toll-like receptor (TLR)—myeloid differentiation primary response 88 (MYD88)—nuclear factor kappa B (NF-κB) pathway. This pro-inflammatory pathway is activated in COVID-19 and leads to severe disease [8]. Besides, statins can increase ACE2 expression, their modulatory effects on lipid raft might decrease severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) entrance into the host cells [9]. These characteristics of statins have been proposed as protective mechanisms against viral infections. For instance, experimental studies have shown that statins can decrease inflammation or prevent virus entry and replication in influenza A virus infection, HIV infection and respiratory syncytial virus (RSV) [10]. Lipid-lowering drugs such as statins frequently prescribed for diabetes, ischemic heart disease, hypertension and stroke. These diseases are prevalently observed in COVID-19 patients and are associated with higher mortality rates, increased intensive care unit (ICU) admission or prolonged hospitalization [11]. In addition statins have been reported to display anti-inflammatory effects that may modify the inflammatory response to the infection. Therefore, in this historical study, we aimed to assess the potential association of exposure to statins and outcomes of hospitalized COVID-19 patients, such as mortality rate, ICU admission, hospitalization length.

Materials and methods

Population enrolment and source of data

This single-center cohort study was performed in Baharloo hospital, a referral hospital for COVID-19 patients in Tehran. Hospitalized patients from February 28, 2020 to October 15, 2020 who were confirmed as COVID-19 patients entered the study. Patients who were less than 20 years of age or received intravenous immunoglobulin (IVIG), remdesivir,

interferon-β (INF-β), tocilizumab, hemoperfusion and extracorporeal membrane oxygenation (ECMO) were excluded from this study. We collected data from patients electronic records for COVID-19 patients. Data information sheet was included, demographic characteristics (age, gender, body mass index [BMI]), their pre-existing conditions (current or former smoker, diabetes, hypertension, stroke, dyslipidemia, cardiovascular diseases and other conditions) and medications (hydroxychloroquine, ribavirin, corticosteroids, ACE inhibitors/ARBs and angiotensin receptor blocker as main medications that other studies showed that can be effective in this group of patients). Mortality, ICU admission and median length of hospitalization was defined as interested outcomes.

All patients were hospitalized due to their moderate to severe clinical manifestations and criteria for detection of COVID-19 was a polymerase chain reaction (PCR) test of the oropharynx or nasopharynx specimen or computed tomography (CT) scan suggesting COVID-19. The study was conducted in accordance with the ethical standards mentioned in the 2013 Declaration of Helsinki. Moreover, the ethical committee of Tehran University of Medical Sciences (TUMS) evaluated the method of this historical study and approved it. After their ethical assessment, the study was granted the ethical code, numbered IR.TUMS.VCR.REC.1399.148.

Hospitalization criteria

Clinical manifestations of COVID-19 in the presence of a positive PCR test or CT scan findings were defined as COVID-19 positive. Expert clinicians assessed CT scans for the presence of radiologic evidence of COVID-19, such as bilateral peripheral or subpleural ground-glass opacities, crazy paving appearance and consolidation [12]. Patients with moderate to severe disease were admitted. These patients came with one or some of the following conditions: decreased O2 saturation (less than 93%), more than 50% involvement of lungs in chest radiography (chest X-Ray or CT scan), dyspnea, labored and shallow breathing and particularly tachypnea (more than 30 breaths per minute), cardiovascular instability and inability to eat because of severe digestive symptoms.

Treatment protocol

Respiratory support was considered for patients with dyspnea or decreased O_2 saturation. Invasive ventilation was provided for a smaller group of patients because their O_2 saturation did not improve with nasal O_2 and non-invasive ventilation (NIV). Additionally, hydration was performed for patients. Symptomatic treatment of fever, pain, diarrhea and vomiting was performed when needed. The distribution of corticosteroids, hydroxychloroquine, ribavirin, ACE inhibitors/ARBs and proton pump inhibitors (PPIs) was assessed among groups and used for adjustment of odds ratio if there was a significant difference.

Groups of patients

Patients were divided into two groups. The first group included patients who did not receive statins. Participants in this group definitely did not use statins recently (within 30 days before admission). The second group included patients who regularly consumed statins because of their pre-existing conditions.

Data analysis

In order to recognize the confounders, we compared the demographic characteristics of patients such as age, sex and body mass index (BMI). Further, we evaluated their pre-existing conditions such as cardiovascular diseases (defined as ischemic heart disease, congestive heart failure and valvular heart disease), hypertension, stroke, diabetes, smoking history, cancer, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis, CKD, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), dyslipidemia, thyroid diseases (hypo- and hyperthyroidism) and history of surgery. In addition, the distribution of drugs such as corticosteroids, hydroxychloroquine, ACE inhibitors and ARBs was assessed. Death rate, ICU admission, and median length of hospitalization were the main outcomes of this study and we compared them between groups. To adjust the effect of confounders, adjusted odds ratio was assessed by logistic regression. The pre-existing conditions, demographic characteristics and utilized drugs were compared between groups. The feature was considered in the adjustment of odds ratio if it had a significantly different distribution among groups. Furthermore, to measure the possible association of statins with inflammation, serum concentrations of inflammation markers such as CRP (C-reactive protein), ferritin, prolactin and LDH (lactate dehydrogenase) were compared between studied groups. The first laboratory results of patients were used for this measurement. Quantitative variables are presented as mean (SD), and qualitative variables are shown as frequencies and percentages. Differences in means were evaluated using the student's t-test. Differences in percentages were measured by the χ^2 test. Stata software version 14 (Stata Corp, USA) was used for statistical analysis of data, and differences were considered significant when $p < 0.05$.

Results

Our study included 710 patients; 163 patients regularly used statins and 547 patients did not use statins during their hospitalization or before hospitalization. Atorvastatin and rosuvastatin were the most common statins in this study. Statins users were significantly older than non-users group. Sex and BMI did not show a significant difference between groups. Also, prevalence of diabetes, hypertension, stroke, cardiovascular diseases, CKD and dyslipidemia were significantly more common in people receiving statins (Table 1). Hydroxychloroquine and PPIs were the most prescribed drugs, followed by corticosteroids, ribavirin and ACE inhibitors and ARBs, respectively. Corticosteroids, PPIs, ACE inhibitors and ARBs showed significantly different distribution among groups (Table 2). Of all patients, 16.8% died in this study. Mortality rate was significantly ($p = 0.021$) higher in statins users compared with non-users (22.7% vs. 15%). Also, statins users had a significantly ($p < 0.0001$) higher ICU admission rate (38.7% vs. 22.3%) and increased length of hospitalization (5(5) days vs. 7(6) days). However, statins users

Table 1 Demographic characteristics of patients and their pre-existing conditions of patients.

	All patients	Statin non-users	Statin users	P value
	(*n* = 710)	(*n* = 547)	(*n* = 163)	
Age	57.01 ± 17.22	53.73 ± 16.86	68.03 ± 13.47	<0.0001
BMI	28.09 ± 6.66	27.91 ± 6.56	28.57 ± 6.92	0.337
Male	408 (57.5)	325 (59.4)	83 (50.9)	0.056
Age more than 60 years	314 (44.2)	194 (35.5)	120 (73.6)	<0.0001
Diabetes	213 (30)	131 (23.9)	81 (49.7)	<0.0001
Hypertension	233 (32.8)	147 (26.9)	86 (52.8)	<0.0001
Stroke	16 (2.3)	9 (1.6)	7 (4.3)	0.045
Current or former smoker	63 (8.9)	43 (7.9)	20 (12.3)	0.212
Dyslipidemia	45 (6.3)	21 (3.8)	24 (14.7)	<0.0001
Cardiovascular diseases[a]	101 (14.2)	35 (6.4)	66 (40.5)	<0.0001
Thyroid disorders[b]	36 (5.1)	28 (5.1)	8 (4.9)	0.914
Respiratory diseases[c]	39 (5.5)	26 (4.8)	13 (8)	0.113
Rheumatologic diseases[d]	11 (1.5)	7 (1.3)	4 (2.5)	0.281
CKD	24 (3.4)	12 (2.2)	12 (7.4)	0.001
Cancer	10 (1.4)	9 (1.7)	1 (0.6)	0.446
History of surgery	159 (22.4)	115 (21)	44 (27)	0.109

Data are presented as number (percentage). Age and BMI are presented as mean (SD). BMI: body mass index; CKD: chronic kidney disease.

[a] Cardiovascular diseases were considered as ischemic heart disease, congestive heart failure and valvular heart diseases.

[b] Thyroid diseases were defined as hyperthyroidism and hypothyroidism.

[c] Respiratory diseases were defined as chronic obstructive pulmonary disease, tuberculosis and asthma.

[d] Rheumatologic diseases were defined as rheumatoid arthritis and systemic lupus erythematosus.

Table 2 Distribution of medications among groups.

	All patients	Statin non-users	Statin users	P value
	(*n* = 710)	(*n* = 547)	(*n* = 163)	
Hydroxychloroquine	556 (78.3)	437 (79.9)	119 (73)	0.061
Ribavirin	126 (17.7)	104 (19)	22 (13.5)	0.106
Corticosteroids	156 (22)	109 (19.9)	47 (28.8)	0.016
ACE inhibitors/ARBs	81 (11.4)	49 (9)	32 (19.6)	<0.0001
PPIs	337 (47.5)	212 (38.8)	125 (76.7)	<0.0001

Data are presented as number (percentage). ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; PPIs: proton pump inhibitors.

had decreased mortality rate in ICU (58.73% vs. 67.21%) (Table 3).

Patients had a similar survival pattern during the first half of their hospitalization, but statins users had lower survival during the second half of hospitalization (Fig. 1). Crude odds ratio and adjusted odds ratio were calculated for participants. Age, sex, diabetes, hypertension, cardiovascular diseases, stroke, dyslipidemia, CKD, corticosteroids, ACE inhibitors, ARBs and PPIs were used as counfounder for adjustment of the odds ratio. However, sex had no significant difference among groups; but because of its importance, it was used for adjustment, as well. According to crude odds ratio statins were associated with increased mortality (95% CI, OR 1.66 [1.07—2.57]), ICU admission (95% CI, OR 2.19 [1.51—3.19]) and prolonged hospitalization (95% CI, OR 2.57 [1.69—3.89]). After multiple adjustments of odds ratio with age, sex, diabetes, hypertension, stroke, dyslipidemia, cardiovascular diseases, CKD, corticosteroids, ACE inhibitors, ARBs and PPIs, statins were not associated with significant differences in mortality (95% CI, OR 0.71 [0.41—1.22]), ICU admission (95% CI, OR 1.05 [0.66—1.66]) and prolonged hospitalization (95% CI, OR 1.30 [0.78—2.17]) (Table 4). Moreover, in examining the inflammatory markers, we found that CRP was significantly (p = 0.043) higher in statins users. Ferritin and LDH were slightly lower in statins users, but it was not significant. In addition, prolactin showed a non-significant increase in statins users (Table 5).

Discussion

The results of studies on the role of statins on COVID-19 symptoms have been contradictory. In some studies, statins appeared an effective treatment for COVID-19 infected

Table 3 Overall outcomes of patients in each group.

	All patients	Statin non-users	Statin users	P value
	(*n* = 710)	(*n* = 547)	(*n* = 163)	
Death	119 (16.8)	82 (15)	37 (22.7)	0.021
ICU admission	185 (26.1)	122 (22.3)	63 (38.7)	0 <0.0001
Death number divided into ICU Admission number (%)	64.32	67.21	58.73	
Median length of hospitalization (days)	6 (5)	5 (5)	7 (6)	<0.0001

Death and intensive care unit (ICU) admission are presented as number (percentage). The median length of hospitalization is presented as median (interquartile range).

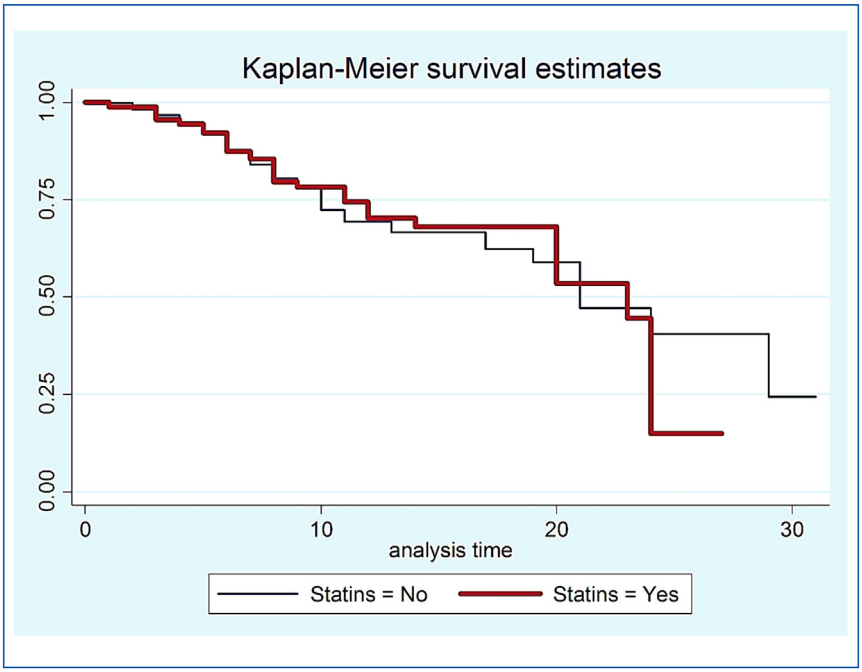

Figure 1. Survival of patients after hospitalization.

Table 4 Crude odds ratio and adjusted odds ratio for outcomes.

	Model 1 odds ratio	*P*-value	Model 2 odds ratio	*P*-value
Outcome: death				
Group 1	1		1	
Group 2	1.66 (1.07—2.57)	0.022	0.71 (0.41—1.22)	0.220
Outcome: ICU admission				
Group 1	1		1	
Group 2	2.19 (1.51—3.19)	< 0.0001	1.05 (0.66—1.66)	0.835
Outcome: prolonged hospitalization (more than median)				
Group 1	1		1	
Group 2	2.57 (1.69—3.89)	< 0.0001	1.30 (0.78—2.17)	0.311

Group 1: Statin non-users (*n* = 547); Group 2 (*n* = 163): Statin users; 95% CI (confidence of interval) was considered for assessment of odds ratio. Model 1: Crude odds ratio; Model 2: Adjustment of odds ratio with age, sex, diabetes, hypertension, stroke, dyslipidemia, cardiovascular diseases, CKD: corticosteroids, ACE inhibitors, ARBs and PPIs; CKD: chronic kidney disease; ACE: angiotensin converting enzyme; ARBs: angiotensin receptor blockers; PPIs: proton pump inhibitors.

Table 5 Inflammatory markers of patients.

	All patients	Statin non-users	Statin users	*P*-value
	(*n* = 710)	(*n* = 547)	(*n* = 163)	
CRP (mg/L)	37.10 (47)	35.30 (46)	42.70 (47)	0.043
Ferritin (ng/mL)	200 (316)	202.40 (300)	165.30 (350)	0.126
Procalcitonin (ng/mL)	0.18 (0.99)	0.18 (0.99)	0.25 (1)	0.828
LDH (mg/L)	471.00 (287)	487 (333)	434.00 (281.51)	0.234

Data are presented as median (IQR). CRP: C-reactive protein; LDH: lactate dehydrogenase.

patients. A retrospective study on 13981 patients in Hubei Province, China, reported that in-hospital use of statins in patients with COVID-19 was associated with decreased all-cause mortality (5.2% mortality rate in statins users vs. 9.4% in non-users) [13]. An American propensity-matched cohort study with 1296 patients reported similar results. The study showed that antecedent use of statins was significantly (95% CI, OR 0.48 [0.36—0.64]) associated with lower inpatient mortality [14]. Another study with fewer patients indicated that statins are associated with decreased ICU admission, but they did not improve other outcomes such as death, hypoxia and the need for intubation [15]. Song et al. revealed that statins use is associated with decreased need for intubation (OR 0.45 [0.20—0.99]), but not with a decrease in mortality or ICU admission [16]. Daniels et al. reported that statins use during the 30 days prior to admission for COVID-19 is associated with faster recovery time and reduced risk of severe COVID-19 [17]. In addition, Saeed et al. observed that the use of statins significantly (HR = 0.88, 95% CI 0.84—0.92, p <0.01) decreased the mortality rate of diabetic patients with COVID-19 and improved their inflammatory markers while statins use did not improve mortality rate among nondiabetic patients [18]. A meta-analysis comprising 22 studies from February 2020 to February 2021 showed a significantly lower mortality rate among statins users (adjusted RR = 0.64, 95% Cl 0.57—0.72, p <0.001) [19].

However, often investigations have reported negative effects of statins in COVID-19 patients. For instance, under rare circumstances, statins can cause liver injury and rhabdomyolysis, which might lead to acute kidney injury (AKI), especially in older patients and those with kidney or liver impairments which are also seen in COVID-19 patients [20]. Another study on COVID-19 patients with diabetes revealed that statins were a risk factor for developing AKI [21]. A multicenter, observational French study (CORONADO study) with 2449 patients indicated that statins are associated with an increased risk of mortality in diabetic patients with COVID-19. The mortality rate within seven days was 12.8% in statins users and 9.8% in non-users (p = 0.02). Additionally, the rate of mortality within 28 days was 23.9% in statins users and 18.2% in non-users (p < 0.001) [22]. Meanwhile, some studies have not reported significant efficacy for the use of statins in infected patients. A meta-analysis of nine original articles in this regard was published on August 20, 2020. Meta-analysis of those articles indicated that statins did not improve the severity outcome (OR 1.64 (95% CI 0.51—5.23) nor mortality OR 0.78 (95% CI 0.50—1.21) [23]. In a nationwide retrospective study with 4842 patients, no statistically significant difference was observed between different types of statins except for some clinical benefit tendency with rosuvastatin. Also, there was no meaningful association between recent statins use and all causes mortality rate (HR = 0.96, 95% CI 0.78-1.18) and severity of COVID-19 (HR = 1.16,95% CI 0.95 to 1.41) [24]. Considering the heterogeneity of results, randomized clinical trials are needed to disclose the ultimate effect of statins on COVID-19 outcome.

In this study, statins were mainly consumed by older patients. Comorbidities such as diabetes, hypertension, cardiovascular diseases, CKD and dyslipidemia were more common in statins users. The high prevalence of these comorbidities can be considered as the main reason for significantly increased mortality rate, ICU admission and prolonged hospitalization in statins users. After adjustment age, sex, pre-existing conditions and drugs, statins were not associated with increased mortality, ICU admission and prolonged hospitalization. Statins were even associated with clinically but not statistically significantly lower in mortality rate (95% CI, OR 0.71 [0.41-1.22]) (Table 4). Larger sample size and higher powerful studying may lenify this finding.

Excessive immune response and uncontrolled release of inflammatory cytokines in COVID-19 patients can lead to respiratory insufficiency as the main cause of death [20]. Statins possess several anti-inflammatory properties. Hence, since the beginning of the COVID-19 pandemic, statins have been proposed as candidates for the treatment of COVID-19 [9]. Previous studies reported that statins could decrease CRP and interleukin 6 (IL6) serum concentration in healthy patients or patients with chronic inflammatory diseases [25]. Statins have the potential to modulate leukocytes function, decrease cytokines release and improve endothelial cells function [26]. However, in this study use of statins was not associated with a decrease in markers of inflammation and even higher levels of CRP concentrations were observed in statins users.

Our study was a historical study and confronted several limitations. We relied on histories of patients for parts of the data. For instance, our data for most of the patients' pre-existing comorbidities were based on patients' histories. There may be several confounders for studies like this that we do not know yet, or we cannot measure them in historical studies. For instance lack of sufficient information about aspirin usage in COVID-19 hospitalized patients.

Besides that, we did not compare different types and doses of statins. Interaction of other drugs that may be given routinely with statins and their effect on COVID-19, such as

aspirin, should also be considered. Maybe, future clinical trials overcome these limitations and uncover the effect of statins on COVID-19 outcomes.

Conclusion

Based on these results, the use of statins did not seem to change outcomes in COVID19. Furthermore, a clinically but not statistically significant decrease was observed in mortality rate. Maybe, larger sample size and higher power of study make it statistically significant. In addition, the use of statins was not associated with a decrease in markers of inflammation in this study.

Funding

This study was financially supported by Tehran University of Medical Sciences (TUMS).

Ethical approval

This study was conducted in accordance with the 2013 version of the Declaration of Helsinki and was approved by the ethics committee of Tehran University of Medical Sciences (TUMS). The ethics committee of Tehran University of Medical Sciences (TUMS) measured the method of this study and approved it, IR.TUMS.VCR.REC.1399.148.

Code availability

The code of the software used in this study will be delivered by a reasonable request.

Data availability

The data analyzed for this study is available in the article.

Consent to participate

Patients were included after obtaining their informed consent.

Consent for publication

Results are reported after obtaining patients' informed consent for publication.

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Disclosure of interest

The authors declare that they have no competing interest.

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