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Coronary artery atherosclerosis in reproductive age group women-an autopsy study

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ABSTRACT

Background: Atherosclerosis is the most common coronary artery disease (CAD). It leads to the blocking of arteries and myocardial infarction (MI). Many studies are focused on men. The aim of this study is to look at the prevalence of coronary atherosclerosis, its severity, and arteries involved in postmortem hearts in reproductive age group women. **Aims and Objectives:** The objectives are (1) to estimate the occurrence of coronary atherosclerosis in reproductive age group women of 15–50 years. (2) To grade the atherosclerosis and stenosis. (3) To determine the cardiac changes associated. (4) To note the most common artery involved. **Materials and Methods:** This study was autopsy-based retrospective study done for period of 3 years. From the autopsy forms, details such as age, gender, cause of death, and gross findings were noted. The sections from the left coronary artery (LCA), right coronary artery, left anterior descending (LAD), and circumflex artery (LCA) were reviewed microscopically to note the atherosclerotic grade and percentage of stenosis. Myocardium was reviewed for associated cardiac changes. Range, frequencies, percentage, and P-value were calculated. $P<0.05$ was taken statistically significant. **Results:** Eighty-seven cases belonging to the reproductive age group of 15–50 years were categorized into 4 age groups. Type V American Heart Association atherosclerosis grade was seen more in women between 35 and 50 years. LAD was the most common artery to be involved. Eight cases showed acute MI. **Conclusions:** Women of reproductive age group should be screened from 3rd decade onwards for CAD.

Key words: Cardiovascular disease; Coronary artery disease; Myocardial infarction

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INTRODUCTION

Coronary artery disease (CAD) is a leading cause of death (COD) in both men and women. The diagnosis and management CAD disease have conventionally been given greater importance in men and possibly postmenopausal women due to the long-held belief that reproductive age group women are at a lesser risk of CAD compared to other adult population cohorts.[1] However, one in three women die of CAD.[1] The prompt diagnosis and critical therapeutic interventions for CAD have a direct correlation with survival outcomes as well as morbidity. Studies have shown that Reproductive age-group women with undiagnosed hypo-oestrogenism of hypothalamic origin have fixed coronary lesions with the difference from women without hypo-oestrogenism being significant.[2] A point to be noted is mortality rates due to CAD are higher in women as compared to age-matched men.[2] A note must be added on atypical presentations of angina which is of greater frequency in women as compared to men thus resulting in delayed or missed diagnosis of CAD.[3] This could directly result in an increase in death rates in women as compared to men due to the absence of timely diagnosis and therapeutic interventions.[4]

Women have greater comorbidities, late presentation to medical care as well as less aggressive investigations and treatment for CAD. Mortality due to CAD is greater in women than in men with comparable variables of age, diabetic status, hypertension, obesity, and other

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comorbidities associated with increased risk of CAD.[1,5] Autoimmune disorders with their known greater incidence in women of reproductive age group may result in a chronic inflammatory state facilitating accelerated atherosclerosis.[1] Pre-eclampsia of pregnancy and gestational diabetes are associated with an increased risk of CAD in later life, including the later part of reproductive period.[6]

In such a scenario where there is already an inherent bias in the delayed investigation as well as less aggressive therapeutic choices physicians make for cardiac-related symptoms in women, it is important to have an evidence-based idea of the actual prevalence of CAD in women in general and those belonging to the reproductive age group in particular.[4]

Autopsy has been a traditional and excellent source of scientific data over the decades. Data obtained from autopsy studies have been used to evaluate numerous factors of patient demographics, risk factors, and specific causes of morbidity and mortality. The aim of this study is to highlight the importance of recognizing CAD prevalence and severity in women of the reproductive age group, which will hopefully contribute to a greater understanding of prophylaxis, diagnostic intervention points, and timely management of CAD with a result in its reduced morbidity and mortality.

Aims and objectives

The aims and objectives of this study are (1) to estimate the occurrence of coronary atherosclerosis in reproductive age group women of 15–50 years. (2) To grade the atherosclerosis and stenosis. (3) To determine the cardiac changes associated. (4) To note the most common artery involved.

SUBJECTS AND METHODS

This is a retrospective observational study material used was archived hematoxylin and eosin (H and E) slides in the department of pathology, Indira Gandhi Medical College and Research Centre, Pondicherry. All autopsy forms received for histopathology examination were reviewed for a period of 3 year from January 01, 2019, to December 31, 2021. The study was approved by the Institutional Ethics Committee (IEC) with approval number (no.392/IEC-33/IGMC and RI/PP-26/2022). After obtaining the approval, the study was conducted. The clinical information provided on the autopsy form; morphological findings as recorded during the grossing of specimen in pathology department were used for the study purpose. Postmortem conducted on women aged 15–45 years was considered for the study. Cases where the heart was autolyzed/not received with other organ were excluded from the study. Left coronary artery (LCA), right coronary artery (RCA), left anterior descending (LAD) artery, left circumflex artery, and myocardial sections from the left ventricle, right ventricle, interventricular septum, and apex were reassessed for the purpose of the study. Following points were noted: Microscopically coronary atherosclerotic lesions were examined and categorized into six groups, according to the American Heart Association (AHA) classification 1995.[7] Types of lesions according to the AHA are: Type I-initial lesion with isolated macrophages, Type II-mainly intracellular lipid and fatty streak, Type III-small extracellular lipid pools, Type IV-core of extracellular lipid, Type V-large lipid core and calcification, and Type VI-hemorrhage and other complications. White, Edwards, and Dry method was used to record the degree of stenosis, to grade the amount of luminal block in arteries, and found to be a good and reproducible method with the degree of interobserver concordance. Percentage of the lumen block up to 25%, stenosis was considered Grade 1, 26–50% block was Grade 2, 51–75% was Grade 3, and 76–100% stenosis was Grade 4.[8] Myocardial changes such as ischemia, fibrosis, and hypertrophic changes were noted.[9]

Statistical analysis was carried out for eighty-seven cases. The data collected were statistically analyzed using SPSS (Statistical Package for the Social Sciences) version 16.0. Variables were summarized using frequency and percentage. The Chi-square test was performed to analyze the categorical variables. Fisher's exact test was utilized for checking the association between categorical variables. $P<0.05$ was considered statistically significant.

RESULTS

A total of 87 cases were studied in the reproductive age group of 15–45 years. The manner of death varied from suicidal which included poisoning, hanging, and drug overdosage, hospital-based due to sepsis, and sudden death to brought dead for various causes such as epilepsy, pneumonia, and wheezing (Table 1).

These cases were further categorized into 4 age groups 15–24 years, 25–34 years, 35–44 years, and 45–50 years. Maximum number of cases were in 35–44 years category with –29 cases. The least number of cases was in the category 15–24 years with 16 cases (Table 2).

Atherosclerosis

RCA atherosclerosis showed significant association in the age group 25–34 years, 35–44 years, above 45 years with P=0.000, 0.001, and 0.000, respectively.

LCA atherosclerosis showed significant association in age group 25–34 years, 35–44 years, above 45 years with P=0.045, 0.001, and 0.001, respectively

Table 1: Cause of death

Cause of death	Frequency (%)
Suicidal/accidental	44 (50.7)
Brought dead/sudden death	22 (25.3)
Pre-existing morbidity	9 (10.3)
Drug overdose and alcohol intoxication	6 (6.9)
Infectious	4 (4.5)
Wasp sting	2 (2.3)
Total	87

Table 2: Age-wise distribution of the cases

Age groups	Frequency (%)
15–24 years	16 (18.4)
25–34 years	23 (26.4)
35–44 years	29 (33.3)
44–50 years	19 (21.8)

LDA atherosclerosis showed significant association in age group 25–34 years, 35–44 years, above 45 years with P=0.001, 0.000, and 0.000, respectively (Figure 1).

LCX atherosclerosis showed significant association in age group 25–34 years, 35–44 years, above 45 years with P=0.005, 0.000, and 0.000, respectively (Tables 3 and 4).

Stenosis

LCA stenosis showed significant association in age group 35–44 years, above 45 years with P=0.017 and 0.032, respectively.

LAD stenosis showed significant association in age group 35–44 years, above 45 years with P=0.009 and 0.016, respectively.

LCX stenosis showed significant association in age group 25–34 years, 35–44 years, above 45 years with P=0.000,0.000, and 0.000, respectively (Tables 5 and 6).

Acute myocardial infarction (MI)

Among cases, eight cases showed features acute MI. Seven cases showed advanced atherosclerotic lesion.

The youngest individual with acute MI was 25 years old; however, she was a known case of hypertrophic obstructive cardiomyopathy. The most common mode of death seven out eight cases was brought dead to causality with alleged history of collapse. Sole case with no fixed coronary lesion had sepsis as COD. The highest atheroma grade as per AHA type was VI with Grade 4 stenosis, who also showed triple vessel coronary disease and was only 33 years old (Figure 2).

Old MI

A total of 12 cases showed features of old MI with fibrotic foci in the myocardium. The age range of this cohort was

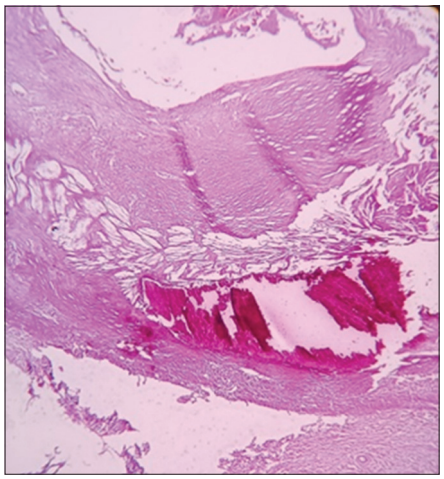

Figure 1: Coronary artery showing American Heart Association Type 5 atherosclerosis

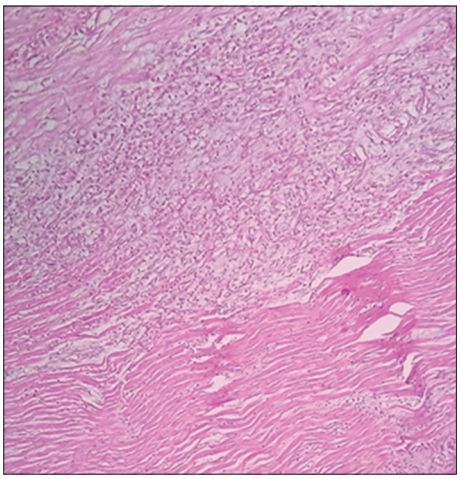

Figure 2: Left ventricle showing features of acute myocardial infarction

15-46 years. Fifteen years old had been brought with alleged sudden death and showed early atherosclerotic lesions in the four coronary arteries studied.

Advanced atherosclerotic lesions (AHA type VI) with significant stenosis (grade 4) were noted in individuals in third decade of life as well as fourth decade of life. The youngest person to show advanced coronary atherosclerosis was 25 years old.

Myocarditis

Both acute and chronic myocarditis as well as were the most frequently seen pathology being noted in 22 cases.

The most common case death in those with myocarditis was poisoning. Moreover, the frequently used poisons were rat killer paste and Organophosphorus compounds. Sepsis with myocarditis and dengue with myocarditis were cases with infection. Two cases with death following wasp sting showed striking eosinophilic myocarditis.

Table 3: AHA atherosclerosis various reproductive age groups in LCA and RCA

AHA staging	15–24 years 16 (n)		25–34 years 23 (n)		35–44 years 29 (n)		45–50 years 19 (n)	
	LCA (%)	RCA (%)	LCA (%)	RCA (%)	LCA (%)	RCA (%)	LCA (%)	RCA (%)
I	5 (31.2)	8 (50)	2 (8.6)	0	1 (3.4)	0	0	0
II	7 (43.7)	7 (43)	11 (47.8)	16 (69.5)	11 (37.9)	16 (55.1)	4 (21.05)	14 (73.6)
III	3 (18.7)	1 (6.25)	5 (21.7)	5 (21.7)	7 (24.1)	4 (13.7)	8 (42)	2 (10.5)
IV	1 (6.2)	0	3 (13)	1 (4.3)	3 (10.3)	5 (17.2)	6 (31.5)	1 (5.2)
V	0	0	1 (4.3)	1 (4.3)	6 (20.6)	2 (6.8)	1 (5.2)	2 (10.5)
VI	0	0	1 (4.3)	0	1 (3.4)	2 (6.8)	0	0
P-value	reference	reference	0.045	0.001	0.001	0.001	0.001	0.001

LCA: Left coronary artery, RCA: Right coronary artery, AHA: American Heart Association

Table 4: AHA Atherosclerosis in various reproductive age groups in LAD and LCX

AHA staging	15–24 years 16 (n)		25–34 years 23 (n)		35–44 years 29 (n)		45–50 years 19 (n)	
	LAD (%)	LCX (%)	LAD (%)	LCX (%)	LAD (%)	LCX (%)	LAD (%)	LCX (%)
I	6 (37.5)	7 (43.75)	0	0	1 (3.4)	0	0	0
II	9 (56.25)	8 (50)	12 (52)	19 (82.6)	10 (34.4)	3 (10.3)	4 (21)	0
III	1 (6.25)	1 (6.2)	9 (39.1)	2 (8.7)	6 (20.6)	14 (48.2)	11 (57.8)	1 (5.25)
IV	0	0	0	0	6 (20.6)	7 (24.1)	2 (10.5)	8 (42.1)
V	0	0	0	1 (4.3)	4 (13.7)	5 (17.2)	1 (5.2)	6 (31.5)
VI	0	0	2	1 (4.3)	2 (6.8)	0	1 (5.2)	4 (21.05)
P-value	reference	Reference	0.001	0.005	0.000	0.000	0.000	0

LAD: Left anterior descending, LCX: Left circumflex artery, AHA: American Heart Association

Table 5: Stenosis grading in LCA and RCA

Stenosis grading	15–24 years 16 (n)		25–34 years 23 (n)		35–44 years 29 (n)		45–50 years 19 (n)	
	LCA (%)	RCA (%)	LCA (%)	RCA (%)	LCA (%)	RCA (%)	LCA (%)	RCA (%)
I	15 (93.75)	15 (93.75)	17 (73.9)	18 (78.2)	16 (55.1)	19 (65.5)	10 (52.6)	14 (73.6)
II	1 (6.25)	1 (6.25)	2 (8.69)	3 (6.2)	5 (17.2)	4 (13.8)	5 (26.3)	3 (15.78)
III	0	0	2 (8.7)	1 (4.3)	2 (6.8)	2 (6.8)	4 (21.05)	0
IV	0	0	2 (8.7)	1 (4.3)	6 (3.44)	4 (13.8)	0	2 (10.5)
P-value	reference	reference	0.124	0.311	0.017	0.009	0.032	0.016

LCA: Left coronary artery, RCA: Right coronary artery

Table 6: Stenosis grading in LAD and LCX

Stenosis grading	15–24 years 16 (n)		25–34 years 23 (n)		35–44 years 29 (n)		45–50 years 19 (n)	
	LAD (%)	LCX (%)	LAD (%)	LCX (%)	LAD (%)	LCX (%)	LAD (%)	LCX (%)
I	15 (93.75)	16 (100)	19 (82.6)	21 (91.3)	14 (48.2)	20 (68.9)	9 (47.3)	14 (73.6)
II	1 (6.25)	0	2 (8.69)	1 (4.3)	5 (17.2)	6 (20.6)	6 (31.5)	1 (5.2)
III	0	0	1 (4.3)	0	5 (17.2)	3 (10.3)	1 (5.2)	3 (15.7)
IV	0	0	1 (4.3)	14 (4.3)	5 (17.2)	0	3 (15.7)	1 (5.2)
P-value	reference	Reference	0.311	0.000	0.009	0.000	0.016	0.000

LAD: Left anterior descending, LCX: Left circumflex artery

Hypertrophy

Twenty cases showed cardiac myocyte hypertrophy. The most common mode of hospital history was "brought dead." The youngest in this age group was 19 years old showed left ventricular free wall hypertrophy. Oldest individuals in this study were 46 years old.

Out of 87 hearts studied, 21 cases showed significant stenosis of more than 50% in at least one artery. Age group of these cases was in 35–50 years. Most of the cases were either brought dead or sudden dead. Among these cases seven of them showed single vessel involvement, 12 cases showed double vessel involvement and two cases showed triple artery involvement.

DISCUSSION

An alarmingly increase in deaths due to coronary atherosclerosis is noted not only in men but also in women of all age groups.[7] Extensive studies mainly concentrate

on women of postmenopausal age group; it is essential to analyze the coronary atherosclerosis in women of the reproductive age group.

The present study was conducted in Pondicherry for a period of 3 years. A total of 87 postmortem hearts were studied in the reproductive age group of 15–50 years. Most studies done in past by Keche et al., Shiladaria et al., Bhargava and Bhargava included both men and women and these studies had predominantly men. Moreover, the percentage of women included was <25%.[10-12]

Type V AHA atherosclerosis was mostly seen in women between 35 and 50 years. The 15–24 years age group showed Type I and II AHA atherosclerosis with no or minimal narrowing of the lumen. In the age group between 25 and 34 years, Type V and IV AHA atherosclerosis and Grade 4 stenosis were noted. Two cases of age 25 years and 33 years, in whom all four vessels showed higher grade atherosclerosis and stenosis.

In the autopsy study, among the women of reproductive age group (age range 15–50 years), 8% had one vessel, 13.7% had double vessels, and 2.3% had triple vessel coronary disease, which is in the same order of frequency as that of Kumar et al.[13] Double vessel disease was more common than the single vessel and triple vessel disease in the present study. In a study done by Beelwal et al., triple vessel disease, followed by double and single-vessel disease.[14]

LAD was the most common artery to be involved, which was also the most common artery involved in studies done by Tabatabaei Yazdi et al., and Sudha et al.[15,16] The observations of the present study showed atheromatous involvement of all major coronary arteries.

Many studies on CAD have been done on men and results are extrapolated to women. Influence of risk factors is different and work differently in men and women.[17]

Plaque erosion is seen more often in young women who smoke and plaque rupture occurs in more common in older women and men with elevated cholesterol levels. Coronary artery calcification is different in both sexes.[18] Atherosclerotic lesion develops as early as 15 years onward. Second decade onward atheroma was significantly noted and there after gradual increase from third decade onwards both in severity and frequency with eight decades showing maximum incidence.[14] Tabatabaei Yazdi et al., observed a sudden increase in atherosclerosis after the second decade and advanced plaque rarely existed under 20 years.[15] Acute MI was seen in eight (9%) cases which were comparable with data given by Beelwal et al., (12.5%) and Maru (6.5%).[19]

The present study showed the prevalence atherosclerosis in women in southern India across various age groups. Although the incidence of atherosclerosis is more in men and postmenopausal women compared to reproductive age group women. There is an alarming increase in CAD in reproductive age group women in India and it is expected to increase more in next decades.

Limitations of the study

The contribution of diabetes millets, hypertension, serum cholesterol, and cigarette smoking could not be assessed as the study was conducted on autopsy cases.

CONCLUSION

The risk factor screening should begin from the early age of the third decade for both men and women. In this study, we highlight the CAD in women of reproductive age group starts as early as third decade. Women of reproductive age group generally get neglected compared to men due to atypical presentation or general belief that women during reproductive age group are generally protected by estrogen. The aim of this study is to highlight screening for CAD in women of reproductive age group.

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REFERENCES

1. Pathak LA, Shirodkar S, Ruparelia R and Rajebahadur J. Coronary artery disease in women. Indian Heart J. 2017;69(4):532-538.
   https://doi.org/10.1016/j.ihj.2017.05.023
2. Bairey Merz CN, Johnson BD, Sharaf BL, Bittner V, Berga SL, Braunstein GD, et al. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: A report from the NHLBI-sponsored WISE study. J Am Coll Cardiol. 2003;41(3):413-419.
   https://doi.org/10.1016/s0735-1097(02)02763-8
3. Ricci B, Cenko E, Varotti E, Puddu PE and Manfrini O. Atypical chest pain in ACS: A trap especially for women. Curr Pharma Des. 2016;22(25):3877-3884.
   https://doi.org/10.2174/1381612822666160309115125
4. Daugherty SL, Blair IV, Havranek EP, Furniss A, Dickinson LM, Karimkhani E, et al. Implicit gender bias and the use of cardiovascular tests among cardiologists. J Am Heart Assoc. 2017;6(12):e006872.
   https://doi.org/10.1161/JAHA.117.006872
5. Maas AH and Appelman YE. Gender differences in coronary heart disease. Neth Heart J. 2010;18(12):598-602.
   https://doi.org/10.1007/s12471-010-0841-y
6. Brewer LC, Svatikova A and Mulvagh SL. The challenges of prevention, diagnosis and treatment of ischemic heart disease

in women. Cardiovasc Drugs Ther. 2015;29(4):355-368.
https://doi.org/10.1007/s10557-015-6607-4

7. Venkatesh K, Deepak DC and Venkatesha VT. Postmortem study of hearts - Pathology of coronary artery atherosclerosis. J Forensic Sci Crim Invest. 2019;12(4):555843.
https://doi.org/10.19080/JFSCI.2018.11.555843
8. White NK, Edwards JE and Dry TJ. The relationship of the degree of coronary atherosclerosis with age, in men. Circulation. 1950;1(4):645-654.
https://doi.org/10.1161/01.CIR.1.4.645
9. Jadhav C, Marak F and Pradeep B. Coronary perivascular adipose tissue inflammation - An autopsy-based histomorphological study from a tertiary care hospital in South India. Asian J Med Sci. 2003;14(1):88-93.
https://doi.org/10.3126/ajms.v14i1.48742
10. Keche AS, Tirpude BH and Bobade HJ. Progressive atherosclerosis in central India - A modern epidemic. Al Ameen J Med Sci. 2013;6(4):342-349.
11. Shiladaria P, Chauhan G, Parghi B, Goswami A and Suri A. Coronary atherosclerosis and myocardial infarction an autopsy study. Natl J Integr Res Med. 2013;4(3):106-108.
https://doi.org/10.70284/njirm.v4i3.2190
12. Bhargava MK and Bhargava SK. Coronary atherosclerosis in North Karnataka. Indian J Pathol Microbiol. 1975;18(2):65-79.
13. Kumar S, Kumar VA, Kumar N, Baranwal RK, Kumar VR and Singh M. Coronary atherosclerosis -- a postmortem histopathological study. Bratisl Lek Listy. 2012;113(4):217-219.
https://doi.org/10.4149/bll_2012_050
14. Beelwal D, Pachori G, Sunaria RK and Goyal V. A post-mortem study of coronary atherosclerosis and relationship to myocardial infarction in Ajmer region. Int J Med Sci Public Health. 2017;6(3):563-567.
https://doi.org/10.5455/ijmsph.2017.0955805102016
15. Tabatabaei Yazdi SA, Rezaei A, Bordbar Azari J, Hejazi A, Taghi Shakeri M and Karimi Shahri M. Prevalence of atherosclerotic plaques in autopsy cases with noncardiac death. Iran J Pathol. 2009;4(3):101-104.
16. Sudha ML, Sundaram S, Purushothaman KR, Kumar PS and Prathiba D. Coronary atherosclerosis in sudden cardiac death: An autopsy study. Indian J Pathol Microbiol. 2009;52(4):486-489.
https://doi.org/10.4103/0377-4929.56130
17. Yahagi K, Davis HR, Arbustini E and Virmani R. Sex differences in coronary artery disease: Pathological observations. Atherosclerosis. 2015;239(1):260-267.
https://doi.org/10.1016/j.atherosclerosis.2015.01.017
18. Sato Y, Kawakami R, Sakamoto A, Cornelissen A, Mori M, Kawai K, et al. Sex differences in coronary atherosclerosis. Curr Atheroscler Rep. 2022;24(1):23-32.
https://doi.org/10.1007/s11883-022-00980-5
19. Maru M. Coronary atherosclerosis and myocardial infarction in autopsied patients in Gondar, Ethiopia. J R Soc Med. 1989;82(7):399-401.
https://doi.org/10.1177/014107688908200710

Authors' Contributions:
CRJ- Design of the study, prepared first draft of manuscript, statistical analysis, and results interpretation; **FM**- Performed autopsy, provided intra-autopsy findings, concept, and coordination; and **BP**- Concept of the study, coordination, reviewed the literature, and revision of the manuscript.

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