

## Original Research Article

# Heart attack encroaching fourth decade: autopsy study of western Maharashtra

Mansi Thokal<sup>1</sup>, Shilpa Narayankar<sup>1\*</sup>, Saurabh Patil<sup>2</sup>

<sup>1</sup>Department of Pathology, Government Medical College, Alibag, Raigad, Maharashtra, India

<sup>2</sup>Department of Radiology, Government Medical College, Alibag, Raigad, Maharashtra, India

**Received:** 30 December 2023

**Revised:** 03 January 2024

**Accepted:** 04 January 2024

### \*Correspondence:

Dr. Shilpa Narayankar,

E-mail: [shilpathology@gmail.com](mailto:shilpathology@gmail.com)

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## ABSTRACT

**Background:** Indians are known to have the highest coronary artery disease (CAD) rates, and the conventional risk factors fail to explain this increased risk. At present, India has the highest burden of acute coronary syndrome and ST-elevation myocardial infarction (MI).

**Methods:** An autopsy study of 6 years: January 2015 to December 2020 which included heart specimens affected by MI from medicolegal autopsies received in histopathology section. The received heart specimens were fixed in 10% formalin and processed as per routine histotechniques with H&E stain and slides prepared were studied under light microscopy.

**Results:** Maximum number of myocardial infarction cases 21 (23.5%) were seen in the age group of 41-50. Commonest histopathological pattern noted was Healed myocardial infarction 38 (42.6%), followed by acute myocardial infarction (AMI) 29 (32.5%) then acute with healed myocardial infarction (AHMI) 22 (24.7%).

**Conclusions:** Atherosclerosis being the most common cause of MI but frequency of non-atherosclerotic myocardial infarction is rising in 4th decade which is a matter of concern. The study of human atherosclerotic lesion is an extremely difficult task in a living subject and an autopsy study is the best possible way to work on it.

**Keywords:** Autopsy study, Atherosclerosis, Coronary artery disease, Myocardial infarction

## INTRODUCTION

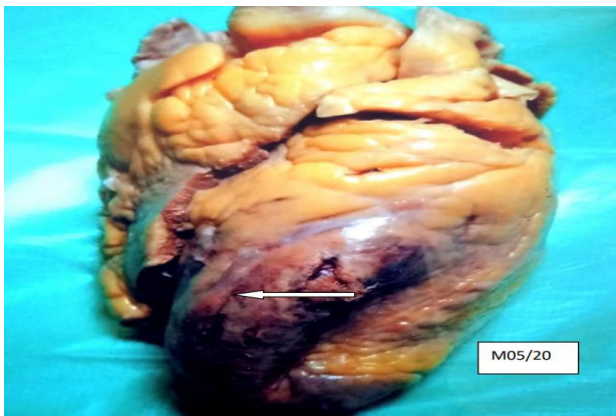
Cardiovascular diseases (CVDS) are the leading cause of mortality and a major contributor to disability. Globally, the estimated number of deaths due to CVDs increased from around 12.1 million in 1990 (equally distributed between males and females) to 18.6 million (9.6 million males and 8.9 million females) in 2019. In accordance with the World Health Organization, India accounts for one-fifth of these deaths worldwide especially in younger population. CVDs strike Indians a decade earlier than the western population. For us Indians, particular causes of concern in CVD are early age of onset, rapid progression and high mortality rate. Indians are known to have the

highest coronary artery disease (CAD) rates, and the conventional risk factors fail to explain this increased risk. At present, India has the highest burden of acute coronary syndrome and ST-elevation myocardial infarction (MI).<sup>1</sup>

An autopsy study gives a good measure of the prevalence, grading and distribution pattern of coronary atherosclerotic lesions and myocardial infarction in the general population. In order to assess the magnitude of ischemic heart disease, a retrospective study of autopsy cases for the presence of atherosclerotic lesions of coronary arteries and associated ischemic cardiac lesions like myocardial infarction (MI) was undertaken for a period of 6 years from January 2015 to December 2020.

## METHODS

The present observational autopsy study was conducted in the department of pathology at Government Medical College, Miraj. In this study, the specimens of heart were studied over a period from January 2015 to December 2020. The study included heart specimens affected by MI from medicolegal autopsies received in histopathology section. The received heart specimens were fixed in 10% formalin. The heart was examined externally to note the size, weight, course of coronary arteries, scars of MI etc. Gross features of MI were recorded. The heart was cut open along the flow of blood as described by Virchow. In few cases in order to demonstrate infarction “Bread loaf technique” of dissecting the heart was employed where the heart was sliced transversely at 1 to 1.5 cm intervals from apex to a point approximately 2.5 cm caudal to the sulcus or up to the midpoint of papillary muscles of the left ventricles. After opening the heart, right and left ventricular free wall thicknesses were recorded. The condition of heart valves, thickness of cusps and calcification were noted. The aorta, right and left coronary arteries, left anterior descending artery and left circumflex coronary arteries were examined for atherosclerosis, presence of any occluding thrombus, aneurysmal dilatation and congenital anomalies. Tissue bits were taken for microscopic study as per the standard protocol. Firstly, the right and left atrio-ventricular areas were chosen to consist of ventricular muscle, atrial muscle and coronary vessels in atrio-ventricular groove. Secondly, the aorta. Thirdly, interventricular septum with the left anterior descending artery.

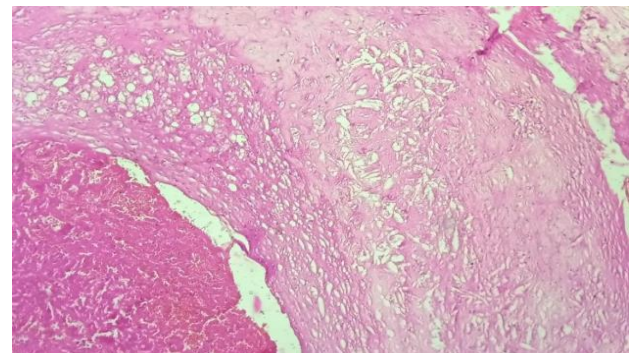


**Figure 1: Gross linear cardiac rupture of left ventricle.**

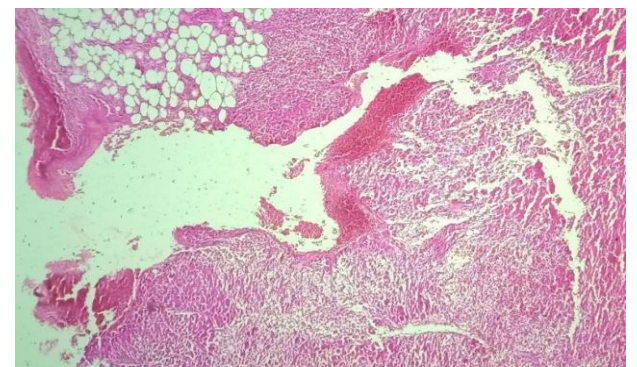
Additional bits were taken from any gross pathological lesion found. Multiple bits from tissue fixed in 10% formalin were processed by routine tissue processing technique and were embedded in paraffin blocks. Tissue sections of 3-5-micron thickness were cut. These sections were stained with routine hematoxylin and eosin stains. The stained sections were mounted with cover slips using DPX as a mountant. The slides thus prepared were studied under light microscope. The sections were studied and correlation of gross and microscopic findings was made.



**Figure 2: Thrombus in LAD and LCx (H&E, x100).**



**Figure 3: Atheroma with overlying thrombus (H&E, x100).**



**Figure 4: Cardiac rupture (H&E, x100).**

The findings were divided into the following categories namely: acute myocardial infarction (AMI), acute with healed myocardial infarction (AHMI), healed myocardial infarction (HMI), and atherosclerotic coronary artery disease (ACAD).

Stary et al classification of atherosclerosis was utilized for classifying atherosclerotic lesions of coronaries.<sup>2</sup> It is a descriptive (observational) study hence for data analysis descriptive statistics were used.

The present study included the histopathological features of MI in medicolegal cases at our institute during a period from January 2015 to June 2020. The total number of heart specimens received in our department was 869. Out of

869; 89 specimens (10%) of heart from myocardial infarction cases were studied during the study period. Frequency of myocardial infarction in autopsies is shown in Table 1.

## RESULTS

Most number of cases 173 autopsies were noted in 2019 with 22 cases (12.7%) of MI. In our study we noted the greatest number of cases were of healed myocardial infarction 38 (42.6%), followed by AMI 29 (32.5%) and AHMI 22 (24.7%) (Table 1).

**Table 1: Frequency of myocardial infarction in autopsies.**

| Year         | No. of cases included in the study (%) | Total medicolegal cases |
|--------------|----------------------------------------|-------------------------|
| 2015         | 15 (8.8)                               | 70                      |
| 2016         | 10 (6.2)                               | 161                     |
| 2017         | 14 (9.5)                               | 157                     |
| 2018         | 20 (12.5)                              | 159                     |
| 2019         | 22 (12.7)                              | 173                     |
| 2020         | 08 (5.3)                               | 149                     |
| <b>Total</b> | <b>89 (10.2)</b>                       | <b>869</b>              |

Maximum number of cases 21 (23.6%) were seen in the age group of 41-50 and least number of cases 02 (2.2%) were noted in 81-90 age group. Males 77 cases (86.5%) were affected more frequently by myocardial infarction as compared to females 12 cases (13.5%) (Table 2). Anterior, antero-septal, antero-lateral were considered in anterior wall group while posterior, posteroseptal, postero-lateral in posterior group. Lateral wall alone constitutes lateral wall group. Anterior wall group accounted for the maximum number of cases 58 (65.1%). Three cases showed involvement of more than one wall. Involvement of right side of heart, especially right atrium 01 (1.1%) is quite rare. Triple vessel disease was most common contributing 66 (74.1%) cases while single vessel disease

was least common with only five (5.6%) cases. In four (4.4%) cases, none of the major coronary arteries showed atherosclerosis. Commonest type of atherosclerosis was type Vb (fibrous plaque with calcification) accounting for 102 cases. The commonest vessel involved was left anterior descending artery with 71 cases (23.4%) (Table 3).

In our study, we came across 29 cases of thrombosis overlying an atherosclerotic plaque-15 cases (16.8%) were seen in LAD, followed by 9 cases (10.1%) in left main coronary LMC. Thrombus associated with AMI was seen in 18 cases. The most common coronary vessel harbouring thrombus was LAD (11 out of 18 cases) 61.1%. AMI was seen in 76% of the cases of triple vessel disease followed by 21% in double vessel disease. Maximum number of cases of AMI, AMI with healed MI and healed MI was observed in triple vessel disease 78%. Atherosclerosis of the coronary vessels is the commonest etiological agent for AMI. Atherosclerosis was assessed in aorta, LMC, LAD, LCx and RCA in every case. Hence total number of vessels assessed for atherosclerosis was 445. Out of these, 304 vessels (68%) showed evidence of atherosclerosis. The most common vessel involved was LAD (71/304, 24%). The details of other vessels involved are as follows: LMC (67/304, 22.1%), LCx (56/304, 18.4%), RCA (59/304, 19.4%) and aorta (51/304, 16.8%). Morphologically the commonest type of atherosclerosis was type Vb i.e. fibroatheroma with calcification, seen in total 102 out of 304 cases (33.5%). Atherosclerosis type Vb was seen affecting LAD in 31 cases, LCx in 25, LMC in 21, RCA in 17 and aorta in 8 cases. Complications of atherosclerosis were noted in 30 cases (33%) out of 89. Type VIc (thrombosis overlying atherosclerotic plaque) was the most common complication accounting for 16 (53%) out of 30 cases. In 10 (33%) cases the thrombus was seen in the LAD. Type VIb (hematoma or hemorrhage) was seen in 8 (26%) cases. Type VIabc (surface rupture, hematoma and thrombosis) was seen in 6 (20%) out of 30 cases.

**Table 2: Demographic data: age and sex distribution pattern of myocardial infarction cases.**

| Age          | Males     | Male (%)    | Females   | Female (%)  | Total (%) |
|--------------|-----------|-------------|-----------|-------------|-----------|
| 21-30        | 12        | 13.4        | 01        | 1.1         | 13 (14.6) |
| 31-40        | 16        | 17.7        | 04        | 5.5         | 20 (22.6) |
| 41-50        | 18        | 20          | 03        | 3.3         | 21 (23.6) |
| 51-60        | 17        | 17.7        | 01        | 1.1         | 18 (20.3) |
| 61-70        | 09        | 10          | 02        | 2.2         | 11 (12.3) |
| 71-80        | 03        | 3.3         | 01        | 1.1         | 04 (4.4)  |
| 81-90        | 02        | 2.2         | 0         | 0           | 02 (2.2)  |
| <b>Total</b> | <b>77</b> | <b>86.5</b> | <b>12</b> | <b>13.5</b> | <b>89</b> |

**Table 3: Distribution pattern of myocardial infarction.**

| Area of heart        | Acute MI | Acute with healed MI | Healed MI | Total (%) |
|----------------------|----------|----------------------|-----------|-----------|
| Anterior wall group  | 22       | 12                   | 24        | 58 (65.1) |
| Posterior wall group | 4        | 7                    | 5         | 16 (18)   |
| Apex                 | 3        | 1                    | 2         | 6 (6.7)   |

Continued.



| Area of heart | Acute MI | Acute with healed MI | Healed MI | Total (%) |
|---------------|----------|----------------------|-----------|-----------|
| IVS           | 0        | 0                    | 3         | 3 (3.3)   |
| Right atrium  | 0        | 0                    | 1         | 1 (1.1)   |
| LV+RV+IVS     | 0        | 0                    | 2         | 2 (2.2)   |
| LV+RV         | 0        | 2                    | 1         | 3 (3.3)   |
| <b>Total</b>  | 29       | 22                   | 38        | 89        |

**Table 4: Pattern of coronary atherosclerosis in myocardial infarction.**

| Type of atherosclerosis | Aorta     | Left main coronary | Left anterior descending | Left circumflex | Right coronary | Total (%)  |
|-------------------------|-----------|--------------------|--------------------------|-----------------|----------------|------------|
| <b>Type i</b>           | 0         | 0                  | 0                        | 0               | 0              | 0          |
| <b>Type ii a</b>        | 4         | 3                  | 0                        | 0               | 1              | 8 (2.6)    |
| <b>Type ii b</b>        | 7         | 5                  | 2                        | 8               | 10             | 32 (10.5)  |
| <b>Type iii</b>         | 20        | 3                  | 5                        | 3               | 10             | 41 (13.5)  |
| <b>Type iv</b>          | 8         | 23                 | 15                       | 13              | 16             | 75 (24.7)  |
| <b>Type v a</b>         | 2         | 6                  | 5                        | 1               | 1              | 15 (4.9)   |
| <b>Type v b</b>         | 8         | 21                 | 31                       | 25              | 17             | 102 (33.5) |
| <b>Type v c</b>         | 0         | 0                  | 0                        | 1               | 0              | 1 (0.3)    |
| <b>Type vi a</b>        | 0         | 0                  | 0                        | 0               | 0              | 0          |
| <b>Type vi b</b>        | 1         | 3                  | 1                        | 1               | 2              | 8 (2.6)    |
| <b>Type vi c</b>        | 1         | 2                  | 10                       | 2               | 1              | 16 (5.2)   |
| <b>Type vi abc</b>      | 0         | 1                  | 2                        | 2               | 1              | 6 (1.9)    |
| <b>Total (%)</b>        | 51 (16.8) | 67 (22)            | 71 (23.6)                | 56 (18.4)       | 59 (19.4)      | 304        |

### Complications of myocardial infarction

We noted 2 cases (2.2%) of ventricular aneurysm, and one case each of free wall rupture and mural thrombosis. Our first patient with ventricular aneurysm was 47 years male with AMI and chronic ischemic heart disease (CIHD) with triple vessel disease. The aneurysm involved the fibrotic area representing healed MI involving left ventricle. The other patient was 57-year-old male, having AMI involving the apex and healed MI involving the lateral wall of left ventricle. He also had triple vessel disease. Aneurysm was seen involving the free wall of LV. In both the cases the wall of the aneurysmal sac was composed of necrotic myocardium replaced by fibrous tissue indicating a true aneurysm. Mural thrombus was not seen in either of the cases. We noted four cases (4.4%) of IHD without atherosclerosis of coronaries. First case: The patient with AMI was 32 years female with chronic hepatitis Ishak grade V, thromboemboli in pulmonary and myocardial vessels and multiple fresh infarcts. Second and third case with chronic ischemic heart disease and normal coronaries had findings suggestive of hypertrophic cardiac myopathy. Fourth case: 34-year-old male. He had history of sudden death during exercise. On gross examination, the heart weighed 480 gms, much above the normal range. The LV free wall thickness was 2 cm while IVS thickness was 3.8 cm. The LV as well as RV showed concentric hypertrophy and fibrous white scar indicating healed infarcts. All the epicardial coronary arteries were normal. On microscopy section from the IVS typically showed myofiber disarray, myocyte hypertrophy, thickening of intramural coronary arteries and fibrosis. Variation in nuclear size with few bizarre nuclei was a prominent feature.

### DISCUSSION

Ischemic heart disease is an important cause of morbidity and mortality both in developed and developing countries. The huge burden of ischemic heart disease in India is a consequence of large population and high prevalence of cardiovascular risk factors like smoking, alcoholism, sedentary lifestyle, obesity, high blood pressure and abnormal lipids and diabetes.<sup>3</sup> The changes in ischemic heart disease cannot be fully revealed during life. A detailed gross study of heart and histological analysis is still the gold standard.

Hence a study of specimens of heart from autopsy cases of myocardial infarction was done to evaluate the prevalence and pattern of atherosclerotic coronary artery involvement in MI and to study the histological features of IHD including MI.

Out of 869 autopsy cases, 89 cases (10%) reported with findings of myocardial infarction. In our study males (86.5%) were more frequently affected than females (13.5%) which is in accordance with Garg et al (80.9%) and Ghag et al (88.8%) explaining cardioprotective effect of estrogen and healthy dietary habits of females.<sup>4,5</sup> Patil et al noted, that maximum cases 209 (51.35%) were in the age of group 31 to 50 years.<sup>6</sup> Ghag et al also noted maximum number of cases 40-49 years of age group (26.84%); while Garg et al noted maximum incidence 88.9% in seventh decade.<sup>4,5</sup> Our finding regarding age group is similar to Ghag et al and Patil et al may be because of study conducted in similar region (Maharashtra).<sup>5,6</sup> Similar dietary, environmental and lifestyle habits may be

the contributing risk factor in this region for early presentation of IHD. It also emphasizes that ischemic heart disease was a disease of elderly but now shifting towards younger age group, which may be because of present urbanization, sedentary life style and changing dietary habits.

Healed infarcts (52.38%) were found to be most common in Ghag et al autopsy study, followed by acute infarcts (23.17%) and acute on healing (0.63%) were least frequent.<sup>5</sup> In our autopsy study, most of the cases presented with healed myocardial infarction 42.6%, Patil et al and Marwah et al also noted similar findings.<sup>6,7</sup> In a study by Pandey et al the most common wall involved was anterior wall which is comparable to the present study.<sup>8</sup> Anterior wall is most predominantly involved area followed by posterior wall and lateral wall, hence it became evident that coronary lesion is always found in an artery which supplies the infarcted myocardium. Our findings are similar with Ghag et al, Garg et al and Pandey et al.<sup>4,5,8</sup> Garg et al noted, incidence of coronary involvement in left anterior descending was 38.1%, right coronary artery 35.1% and left circumflex artery 34%; while Ghag et al and we also noted similar finding.<sup>4,5</sup> The most frequent cause of acute myocardial ischemia is atherothrombotic occlusion of a coronary artery.<sup>9,10</sup> The presence of a mural or totally occlusive thrombotic mass can be observed at autopsy in approximately 50–70% of sudden coronary deaths and is a reliable marker of myocardial ischemia, even in absence of microscopically visible necrosis.<sup>10,11</sup> Left anterior descending artery (LAD) was the commonest site for plaque formation. LAD provides the major blood supply to the interventricular septum, and thus bundle branches of the conducting system. Hence, blockage of this artery due to coronary artery disease can lead to impairment or death (infarction) of the conducting system. The result is a "block" of impulse conduction between the atria and the ventricles known as "right/left bundle branch block". Marwah et al, Patil et al and Soyemi et al also noted that the left anterior descending artery was commonly involved in atherosclerotic Myocardial Infarction followed by right coronary and left circumflex artery.<sup>6,7,12</sup>

In our study triple vessel involvement was the commonest (78%) followed by double (14%) and single vessel (5%) involvement. It was well correlated with the study given by Garg et al, Ghag et al, Marwah et al and Porwal et al.<sup>4,5,7,13</sup> However, the works of Dhruwa et al, and Virmani et al, gave a different pictures and showed single vessel involvement was the most common.<sup>14,15</sup> Marwah et al stated that, the ischemic heart disease was found to be the leading cause of death with coronary atherosclerosis being the most significant pathogenetic mechanism and three vessel disease the most common pattern of involvement.<sup>7</sup>

Ghag et al noted complications of myocardial infarction in 38 cases (12%).<sup>5</sup> Most common complications was ventricular dilatation in 17 cases (5.3%) followed by mural thrombus 15 cases (4.7%). We noted complications of myocardial infarction in 4.5% of cases with ventricular

dilatation (2.2%) being the commonest complication followed by free wall rupture in one case (1.1%) and mural thrombus (1.1%) in other. Cardiac rupture is a rare but critical complication of myocardial infarction with an incidence of 1 to 3% of cases.<sup>16</sup> Sakda et al concluded that myocardial infarction in patients with normal coronary artery had multifactorial etiologies, including toxicological factors such as alcohol and drugs.<sup>17</sup> He also pointed out that the subjects in a non-atherosclerotic group were younger than an atherosclerotic one with mean age of the cases was 33±12 years old. We also noted non-atherosclerotic myocardial infarction in younger age group (30 to 34 years).

### Limitations

A major limitation in this study is the absence of the premorbid states and clinical history of these patients. Since, most were brought-in-dead (BID) or found dead, information such as lipid profile, homocysteine levels, antihypertensive drug usage, anti-lipid drugs compliance or hypoglycaemic agents were unknown.

### CONCLUSION

Risk of MI is alarming in Western region of Maharashtra in younger population showing high prevalence in 40-49-year age group. Atherosclerosis being the most common cause of MI but frequency of nonatherosclerotic myocardial infarction is rising in 4<sup>th</sup> decade which is a matter of concern. The study of human atherosclerotic lesion is an extremely difficult task in a living subject and an autopsy study is the best possible way to work on it. Our study aids valuable data to the literature regarding the morphology of atherosclerotic lesion and its relation to the significant cardiac lesion. The knowledge about the time trends and the morphological features of ischemic disease can guide the possible preventive measures. Thus, extensive cross-sectional studies depicting the histomorphological details are needed to tackle the impending epidemic of myocardial infarction.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

### REFERENCES

1. Kumar S, Sinha N. Cardiovascular disease in India: A 360 degree overview. Med J Armed Forces India. 2020;76(1):1-3.
2. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W Jr, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation. 1995;92(5):1355-74.

3. Park K. Epidemiology of chronic non-communicable diseases and conditions. Park's Textbook of Preventive and Social Medicine. 25rd edition. Jabalpur: Banarasidas Bhanot Publishers. 2019;405.
4. Garg M, Aggarwal A, Kataria S. Coronary atherosclerosis and Myocardial Infarction An autopsy study. *J Indian Acad Forensic Med.* 2011;33:39-42.
5. Ghag M, Kulkarni D. Histomorphological evaluation of myocardial infarction: autopsy study. *Indian J Basic Appl Med Res.* 2018;7(2):201-7.
6. Patil RN, Dani AA, Raut UH, Chaturkar AR, Kumbhalkar DT. Study of coronary atherosclerosis and myocardial infarction in medico legal autopsies from Central India. *J Evid Based Med Healthc.* 2020;7(36):1908-12.
7. Marwah N, Sethi B, Gupta S, Duhan A, Singh S, Sen R. Histomorphological Spectrum of Various Cardiac Changes in Sudden Death: An Autopsy Study. *Iranian J Pathol.* 2011;6(4):179-86.
8. Pandey S, Jhanwar P, Jhanwar S. A prospective study of Myocardial Infarction patients admitted in a tertiary care hospital of south-eastern Rajasthan. *Int J Biol Med Res.* 2012;3(2):1694-6.
9. Basso C, Aguilera B, Banner J, Cohle S, d'Amati G, de Gouveia RH, et al. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. *Virchows Arch.* 2017;471(6):691-705.
10. Davies MJ. Anatomic features in victims of sudden coronary death. *Coronary artery pathology.* *Circulation.* 1992;85:119-24.
11. Farb A, Tang AL, Burke AP, Sessums L, Liang Y, Virmani R. Sudden coronary death. Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. *Circulation.* 1995;92(7):1701-9.
12. Soyemi SS, Faduyile FA, Osuolale FI. Fatal Myocardial Infarction: A Retrospective Autopsy Study. *J Clin Diagn Res.* 2018;12(1):EC14-7.
13. Porwal V, Khandelwal S, Jain D, Gupta S. Histological Classification of Atherosclerosis and Correlation with Ischemic Heart Disease: An Autopsy based Study. *Ann Pathol Lab Med.* 2016;3(2):100-4.
14. Dhruva GA, Agravat HA, Sanghri Ak. Atherosclerosis of coronary arteries as predisposing factors in myocardial infarction. An autopsy study. *Online J Health Sci.* 2012;11(3):01-4.
15. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: A comprehensive morphological classification scheme for atherosclerotic lesion. *Arterioscler Thromb Vasc Biol.* 2000;20(5):1262-75.
16. Wehrens XH, Doevendans PA. Cardiac rupture complicating myocardial infarction. *Int J Cardiol.* 2004;95(2-3):285-92.
17. Sathirareuangchai S, Phuangphung P, Poriswanish N. Myocardial infarction without coronary atherosclerosis: Pathological aspect. *Asian Arch Pathol.* 2015;11(3):71-9.

**Cite this article as:** Thokal M, Narayankar S, Patil S. Heart attack encroaching fourth decade: autopsy study of western Maharashtra. *Int J Res Med Sci* 2024;12:422-7.