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Original Article

Metabolic risk factors in first acute coronary syndrome (MERIFACS) Study

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ABSTRACT

Objectives: In acute coronary syndrome (ACS) patients the focus is on major conventional risk factors - CRF [diabetes, hypertension, elevated low-density cholesterol (LDL-C) and smoking] whereas others - specific metabolic risk factors - MRF [high-density lipoprotein cholesterol (HDL-C), body-mass index (BMI), waist-hip ratio (WHR), and triglycerides, and HbA1c get less attention.
Methods: This is a prospective case–control observational study from 15 tertiary care hospitals in India. CRF and MRF in patients presenting with first incidence of ACS ($n = 2153$) were compared with matched controls ($n = 1210$).
Results: Propensity score matching (PSM) yielded 1193 cases and matched 1210 controls. Risk factor prevalence in cases vs. controls were **CRF**: hypertension - 39.4% vs 16.4% ($p < 0.0001$), diabetes - 42.6% vs 12.7% ($p < 0.0001$), smoking - 28.3% vs 9.3% ($p < 0.0001$) and elevated LDL-C - 70.2% vs 57.9% ($p < 0.0001$). **MRF**: High BMI - 54.7% vs 55.1% ($p = 0.84$), increased waist: hip ratio 79.5% vs 63.6% ($p < 0.0001$), high HbA1c - 37.8% vs 14.9% ($p < 0.0001$), low HDL-C - 56.2% vs 42.8% ($p < 0.0001$) and elevated triglycerides - 49.7% vs 44.2% ($p = 0.007$). Adjusted Odds ratios by multivariate analysis were CRF: hypertension - 2.3 ($p < 0.001$), diabetes - 4.7 ($p < 0.001$), high LDL-C - 3.3 ($p < 0.001$) and smoking-6.3 ($p < 0.001$). MRF: High waist: hip ratio - 2.4 ($p < 0.001$) high HbA1c - 3.2 ($p < 0.001$), low HDL-C 2.2 ($p < 0.001$) and elevated triglycerides - 0.878 $p = 0.17$.
Conclusion: In India, the risk of ACS conferred by specific metabolic risk factors (High waist: hip ratio, Low HDL-C and High HbA1c) is comparable to that caused by CRF.

1. Introduction

Prevalence of coronary artery disease (CAD) in India is progressively increasing as shown by data that cardiovascular diseases (CVDs) were accountable for 28.1% of total deaths and 14.1% of total disability-adjusted life years (DALYs) in 2016, compared to 15.2% and 6.9%, respectively, in 1990.[1–3] In routine clinical practice focus is generally directed to the assessment and control of major

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Abbreviations

CVD	Cardiovascular disease
CRF	Conventional Risk Factors
MRF	Specific Metabolic Risk Factors
CAD	Coronary Artery Disease
ACS	Acute Coronary Syndrome
LDL- C	Low-Density Lipoprotein Cholesterol
HDL- C	High-Density Lipoprotein Cholesterol
BMI	Body Mass Index
W:H Ratio	Waist: Hip Ratio
MS	Metabolic Syndrome
NSTEMI	Non-ST-segment Elevation Myocardial Infarction
STEMI	ST-segment Elevation Myocardial Infarction
LVEF	Left Ventricular Ejection fraction
GFR	Glomerular Filtration Rate
ICCU	Intensive coronary care unit

conventional risk factors (CRF) - diabetes, hypertension, elevated low-density cholesterol (LDL-C) and smoking. However these conventional risk factors alone appear insufficient to explain the higher risk of acute coronary syndrome in India. We hypothesize that certain designated specific metabolic risk factors (MRF) such as the low level of high-density lipoprotein cholesterol (HDL-C), increased body-mass index (BMI), waist-hip ratio (WHR), triglycerides, and inadequately controlled diabetes (defined as glycosylated haemoglobin [HbA1c] >7%) also significantly contribute to the risk but does not get due attention in the routine clinical practice when compared to the CRFs. For instance HbA1c is less commonly used for screening and diagnosis of diabetes due to the higher out-of-pocket expenses when compared to the fasting and post-prandial blood sugar levels. These factors necessitate a regional study for a more thorough understanding of a wide range of risk factors in order to develop and implement an effective plan for the prevention and treatment of cardiovascular diseases. Therefore we conducted this study with the objective of demonstrating the importance of specific metabolic factors (MRF) and showing them to be equally predictive of increased risk of acute coronary syndrome as traditionally used conventional factors (CRF).

2. Methodology

2.1. Study design, setting and sample size

This is a multi-centre, case–control, observational study, conducted in India where patients and controls were recruited from 15 participating centers between 2019 and 2020.

1
Participating centers from India - PI & Coordinators

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10. STAR Hospital, Vizag, AP. Sudheer Chandra Sinha, Kotipally Vidya Sagar
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12. Miot Hospital Chennai, Tamilnadu. Jaishankar K, H.Veena
13. Teerthanker Mahavir Hospital, New Delhi. Geethesh Manik, Bhumesh
14. Lisie Hospital, Kochi, Kerala. Jabir Abdullakutty, Liya Rarichan, Dr.Anju Paulose
15. Indo American Hospital, Hyderabad, Telangana. K.Sarath Chandra, Raj Kumar

Ethics approval for the study was obtained from each centre from the Institutional Ethics Committee. Written Informed consent was obtained from all participants. The study was conducted in accordance with the declaration of Helsinki (Fortaleza, 2013) and the national ethical guidelines for biomedical and health research involving human participants (Indian Council of Medical Research, 2017). There are limited studies in the Indian population to assess the prevalence of risk factors and their pattern in acute coronary syndrome patients. However, according to the CADY registry by Iyengar et al, 68% of the 997 consecutive patients recruited in the research had ACS, so with this projected frequency, we required a minimum of 1317 cases (99.99% confidence interval ± 5%) to be enrolled for the study.[4]

2.2. Eligibility criteria

Patients of age ≥18 years diagnosed with the first episode of acute coronary syndrome presenting within 24 h of symptom onset were included in the study. These patients presented with chest pain and had ST-segment Elevation Myocardial Infarction (STEMI), or Non-ST-segment Elevation Myocardial Infarction (NSTEMI). STEMI was defined as ST-segment elevation in two contiguous leads with or without reciprocal ST-segment depression and NSTEMI was defined as serial troponin or CK-MB elevation, with ST-segment depression or T-wave inversion in two contiguous leads.[5,6]

Controls were patients who visited the out patient department of the study sites for routine health check-ups during the study period with no symptoms suggestive of CAD and not on any anti-platelets. Patients who had a prior myocardial infarction (MI) or ACS (treated/untreated), or had undergone a revascularization procedure (PCI or CABG) in the past were excluded from both cases and control groups.

2.2.1. Study procedures

After obtaining informed consent, demographic and clinical data were collected using case record forms. The socio-economic class was assessed as per the modified Kuppuswamy scale.[7] Information about risk factors was obtained by a standardized protocol and laboratory measurement. Weight in kilograms (kg) and the height in centimeters (cm), were measured using calibrated weighing scales and stadiometers respectively before being transferred out of ICCU. Waist and hip circumferences (HC) were measured with a non-stretchable standard and calibrated measuring tape. Waist measurements were obtained over the unclothed abdomen at the narrowest point between the costal margin and iliac crest, and hip circumferences over light clothing at the level of the widest diameter around the buttocks. Cases and controls underwent routine investigations which specifically included fasting lipid profile, HbA1c and 2 d echocardiogram.

Centers were directed to take fasting samples and withdraw venous blood from cases within 24 h of presentation with acute coronary syndrome. Total cholesterol and triglyceride levels were measured using an automated analyzer and LDL was calculated using the Friedewald formula when serum triglycerides were less than 400 mg/dl. Triglycerides were estimated by GPO-POD method, LDL and HDL by enzymatic colour test. HbA1c was assessed by Ion-exchange high-performance liquid chromatography. All laboratory measurements across the participating centers were standardized and quality control was maintained by the principal coordinating centre. 2D trans-thoracic echo was performed by an independent observer in all cases. The left ventricular end-diastolic, end-systolic volumes and left ventricular ejection fraction were assessed by biplane Simpson's equation using the apical four and two-chambered views. Data were tabulated and then sent to the major coordinating centre on a weekly basis, where it was organized and subjected to quality check and analysis. Reperfusion and revascularization of patients were done as per the policies and guidelines followed by the treating institutions.

3. Definitions

For the purpose of this study risk factors were classified into.

A. **Conventional Risk Factors (CRF)**:

1. Hypertension: The patient was diagnosed with high blood pressure for a blood pressure reading ≥130/85 mm Hg (by 3 readings) or if a previous diagnosis of hypertension had been made and/or treatment had already been prescribed at the time of admission.[8]
2. Diabetes Mellitus: The diagnosis of diabetes mellitus was made in accordance with the 2018 ADA guidelines for new cases (Fasting blood glucose ≥126 mg% or HbA1c ≥ 6.5 g%) or based on prior diagnosis and treatment by a physician.
3. Elevated LDL-C: As per the recommendations of the National lipid association we categorized those with LDL-C levels ≥100 mg% as high.[9]
4. Smoking: We defined current smokers as individuals who smoked/consumed any tobacco in the previous 12 months and included those who had quit within the past year. Former smokers were defined as those who had quit more than a year earlier. Current smokers and ex-smokers were categorized as smokers in this study.[10]

B. **Specific Metabolic Risk Factors (MRF):**

In this study, we used the following metabolic factors.

1. BMI: The body-mass index (BMI) was calculated using the formula: Body weight (kg)/height^2 (m^2). A value ≥ 25 kg/m^2 was considered high as per the international classification.
2. Waist: Hip Ratio: The cut-off values were ≥0.9 for men and ≥0.85 for women as per WHO definition and INTERHEART Study.[11]
3. HDL-C ≤ 40 mg% in men and ≤50 mg% in women were considered low.
4. Hyper triglyceridemia: Triglyceride levels were considered high for values ≥ 150 mg%.
5. HbA1c ≥ 7, indicating uncontrolled diabetes, as per the glycemic targets of the American Diabetes Association.[12] We particularly used these cut-off values as these are clinically used by physicians for treating patients.

4. Statistical analysis plan

The demographic characteristics and clinical characteristics of cases and controls were summarized using descriptive statistics. Normal distribution was confirmed using the Kolmogorov Smirnov test. The groups were assessed for differences using the chi-squared test for categorical variables and the independent *t*-test for continuous variables. A propensity score matching (PSM) was done using the fuzzy matching technique with a match tolerance of 0.001% for age and gender. The odds ratio was computed for differences in the prevalence of conventional and metabolic risk factors between groups before and after propensity score matching and their statistical significance was assessed using the chi-square test. A multivariate analysis using the binary logistic regression enter method was done with all the metabolic and conventional risk factors in a single model and adjusted odds ratios were computed. Receiver operator characteristic curves were plotted for all the risk factors in the form of continuous variables. Statistical significance was set at $p < 0.05$ for all computations. All relevant data of each participant were recorded in a specially designed case record form. Data entry was done in Microsoft Excel (Publisher: Microsoft Corporation, Redmond, Washington, USA, 2016) and analysis was performed with IBM SPSS Statistics for Windows, Version 25.0 (Publisher: IBM Corp., USA, 2017).

5. Results

The present case–control study included 2153 cases and 1210 controls from 15 participating centers across the country over a period of 18 months starting January 2019.

5.1. The patient cohort

Of the 2153 patients with acute coronary syndrome, 1801 (83.7%) were diagnosed with STEMI while the remaining 352 (12.3%) had NSTEMI. There were 1648 (76.5%) males and 505 (23.5%) were females. The mean age of the cohort was (56 0.11 ± 11.63 years, Range 19–90 years). Males were relatively younger than women (54 ± 11.81 vs 59.50 ± 10.65 years; $p < 0.0001$). A large number of patients 1692 (78.6%) were categorized as middle class as per the Kuppuswamy scale. The comparative demographics of cases and controls are summarized in Table 1. As shown in the table, there was almost equal representation of the rural and urban populations.

After propensity score matching the total number of matched cases and controls were 1193 and 1210. The mean age of the study participants in the matched cases and control groups were 52.57 ± 11.21 years and 52.60 ± 11.32 years respectively. The number of men in the matched cases and control groups was $n = 887$ (74.4%) and $n = 896$ (74.1%) respectively.

5.2. Risk factors - conventional and metabolic

The frequency of CRF and MRF amongst cases and controls and their mean values are shown in Table 2.

The unmatched acute coronary syndrome population ($n = 2153$) had a high prevalence of CRF (93%). The CRF observed were hypertension in 898 (41.7%), diabetes in 940 (43.7%), smoking in 637

Table 1
Demographics.

	Cases (N =2153)	Controls (N =1210)
Gender (M:F)	1648 : 505	896 : 314
Mean Age (years ± SD)	56.11 ± 11.63	52.6 ± 11.32
Rural	1143 (53.1%)	650 (53.7%)
Urban	1010 (46.9%)	560 (46.3%)
Education		
No education	737 (34.2%)	406 (33.6%)
High school or lower	467 (21.7%)	255 (21.0%)
Graduate	237 (11%)	135 (11.2%)
Postgraduate and above	712 (33.1%)	414 (34.2%)
Socioeconomic status(Kuppuswamy scale)		
Upper	47 (2.2%)	15 (1.2%)
Upper Middle	1157 (53.7%)	623 (51.5%)
Lower Middle	535 (24.8%)	324 (26.8%)
Upper Lower	376 (17.5%)	225 (18.6%)
Lower	38 (1.8%)	23 (1.9%)
Annual Income (USD)		
<1000	101 (4.6%)	52 (4.2%)
1001- 5000	1571 (73%)	848 (70%)
5001-10000	429 (19.9%)	270 (22.3%)
10,001- 50,000	105 (4.8%)	43 (3.5%)
Clinical Profile		
STEMI	1801 (83.7%)	N/A
NSTEMI	352 (12.3%)	N/A
Anterior wall STEMI	991 (55%)	N/A
Inferior/Posterior wall STEMI	644 (35.8%)	N/A
STEMI other areas	165 (9.2%)	N/A
Time to presentation (Hours)	8.3 ± 11.3	N/A
Thrombolysis	597 (33.1%)	N/A
Primary PCI	689 (38.3%)	N/A
No reperfusion	515 (28.6%)	N/A
Coronary angiogram	2122 (98.6%)	N/A
Single vessel disease	822 (38.7%)	N/A
Two vessel Disease	648 (30.5%)	N/A
Three vessel disease	526 (24.8%)	N/A
Insignificant lesions	126 (6%)	N/A
LVEF (%)	45 ± 10	64 ± 6
GFR	68 ± 11	69 ± 10
Survival to discharge	2028 (94.1%)	N/A

(29.5%), and elevated LDL-C in 1151 patients (53.5%). All the CRF were higher in cases and were univariate and multivariate predictors of acute coronary syndrome. In comparison to controls, proportion of patients with 1 or more CRF was 93% vs 7% ($p < 0.0001$) those with 2 or more CRF were 61.5% vs 16.7% ($p < 0.0001$) and those with 3 or more were 22.9% vs 4% ($p < 0.0001$) (Table A, Appendix).

The prevalence of MRF in patient group too was high (97%). The MRF seen were abnormal values of BMI in 1133 (52.6%), Waist-Hip ratio (W:H ratio) in 1641 (76.2%), HbA1c in 787 (36.6%), Triglycerides in 557 (25.9%) and HDL-C in 1182 (54.9%). All the MRF except BMI were higher in cases and were univariate predictors of acute coronary syndrome. Multivariate analysis showed only waist: hip ratio, HbA1c and HDL to be predictors while triglycerides and BMI were not. Comparative distribution of MRF amongst cases and controls showed at least 1 MRF in 97.5% vs 89.8% ($p < 0.0001$) 2 or more MRF in 77.1% vs 58% ($p < 0.001$) and 3 or more in 41.8% vs 14.6% ($p < 0.00001$) (Table A, Appendix).

The comparison of risk factors after propensity score matching and multivariate analysis is shown in Fig. 1. It clearly demonstrates the relative closeness of adjusted odds ratios of different CRF and MRF (Data on specificity and sensitivity, positive and negative predictive values for combination of different risk factors in both genders are given in Appendix Tables B and C).

6. Discussion

This is a multi-center observational study of acute coronary syndrome patients and matched controls. This study shows the relative significance of MRF versus CRF in these patients. This investigation demonstrated two major findings.

Firstly, patients with acute coronary syndrome have a high prevalence of specific metabolic risk variables that are comparable to conventional risk factors (97.3% vs 93.3%). Secondly, in these patients' abnormal values - HbA1c, HDL, and waist - hip ratio are individually as important as conventional factors. Studies from India have shown that constitution of the acute coronary syndrome population has consistently differed from that of the western world.[2,13,14] Our research confirms that these disparities have persisted over time, prompting regional studies on the risk factors for coronary artery disease. The patients in our study were relatively young with a mean age of 56 years. In this population, 36% of males and 25% of females were under 50 years of age with 9.2% being under 40 years. Further, the acute coronary syndrome in our population appears to constitute a high-risk substrate as seen by the fact that STEMI was the predominant clinical presentation with only 16.3% of our patients having NSTEMI. This is different from published literature predominantly from the western world, where NSTEMI is more prevalent. It is speculative if the risk factor profile with a high prevalence of MRF influences this difference.

Table 2
Conventional & Metabolic Risk Factors (Propensity matched).

Risk Factors	Cases ($n = 1193$)	Controls ($n = 1210$)	p Value (OR)
Hypertension	470 (39.4%)	199 (16.4%)	<0.0001 (3.64)
Smoking	338 (28.3%)	112 (9.3%)	<0.0001 (4.17)
Diabetes	508 (42.6%)	180 (14.9%)	<0.0001 (5.31)
High LDL-C	838 (70.2%)	700 (57.9%)	<0.0001 (0.62)
High BMI	653 (54.7%)	667 (55.1%)	0.84 (0.81)
High Waist: Hip ratio	949 (79.5%)	769 (63.6%)	<0.0001 (1.97)
Low HDL-C	671 (56.2%)	518 (42.8%)	<0.0001 (1.71)
High HBA1c	451 (37.8%)	154 (12.7%)	<0.0001 (3.34)
HighTriglyceride Levels	1071 (49.7%)	535 (44.2%)	0.007 (1.25)
Mean Values			
Mean LDL (mg/dl)	120 ± 36.6	99.39 ± 39.06	<0.0001
Mean BMI	25.2 ± 4.1	25.5 ± 3	0.05
Mean WH ratio Value	0.91 ± 0.04	0.86 ± 0.04	<0.0001
Mean HBA1c	7.02 ± 1.91	6.0 ± 1.1	<0.0001
Mean HDL-C (mg/dl)	38.2 ± 10.4	41.7 ± 10.4	<0.0001
MeanTriglycrides (mg/dl)	173 ± 86.6	156.54 ± 74.50	<0.0001
Triglycerides/HDL-C	2.8 ± 1.8	2.1 ± 0.8	<0.0001

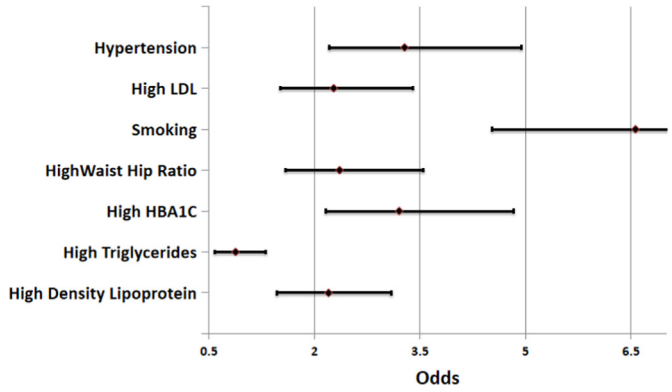

Fig. 1. Forest plot depicting the odds ratios of conventional and metabolic risk factors after multivariate analysis by binary logistic regression. The odds ratios depicted are after adjusting for age and gender

Characteristics	Adjusted odds ratio (a OR)	95% Confidence Intervals	*P* value
Hypertension	3.280	2.630 - 4.091	<0.001
High LDL-C	2.274	1.864 - 2.775	<0.001
Smoking	6.563	5.011 - 8.594	<0.001
High Waist Hip Ratio	2.358	1.911 - 2.911	<0.001
High HBA1C	3.203	2.565 - 4.001	<0.001
High Triglycerides	0.878	0.728 - 1.048	0.172
Low HDL-C	2.201	1.825 - 2.201	<0.001

Large case–control studies have established the role of different risk factors in contributing to the occurrence of myocardial infarction and coronary artery disease. INTERHEART was a global study conducted in 262 centers across 52 countries in patients with acute myocardial infarction, where 9 easily measured risk factors were associated with more than 90% risk of myocardial infarction. Smoking, diabetes, hypertension, abdominal obesity, psycho-social index, and Apo B/Apo A1 ratio contributed to the risk of myocardial infarction while exercise and consumption of fruits and vegetables were protective.[10] A regional sub-analysis of this study (15 centers from 5 south Asian countries) constituting 1732 of the 15,152 cases showed that these risk factors were equally important in this subcontinent.[15] The data demonstrated that the increased burden of harmful factors and decreased prevalence of protective factors accounted for the earlier age of acute myocardial infarction in these countries. Among the various risk factors, the contribution of metabolic factors to the occurrence of clinical events related to CAD is well recognized, however these are in general considered as a cluster of parameters described as Metabolic Syndrome (MS).[16] There is particularly a higher prevalence of metabolic syndrome in India in relation to CAD that has been documented in a few studies.[17,18] Globally the largest study published study establishing metabolic syndrome as a risk factor for acute myocardial infarction is the INTERHEART study[11,19] The utility of metabolic syndrome is more relevant for population-based data rather than for the clinician who deals with an individual patient in view of lack of consensus on terminology and thresholds of individual components.[20–22] In this context the role of individual metabolic factors in clinical practice has been highlighted in an insightful perspective by Reaven.[23]

Our study highlights the importance of a few selected clinically relevant risk factors in acute coronary syndrome patients. The relative importance of these metabolic factors is shown by the close proximity of their adjusted odds ratios to that of the standard conventional factors used in routine clinical practice. The results show that each risk factor is individually important in contributing to the risk of acute coronary syndrome.

The findings of this study highlight the need for expanding the list of coronary risk factors to include MRF and that these are accorded equal weightage as conventional risk factors in terms of

population screening and intervention. A fact of the concern is the high prevalence of metabolic factors in the control population and, unintervened a large number of them may develop clinical coronary artery disease or acute coronary syndrome. This fact thus opens up the urgent need to introduce preventive algorithms to impede this natural and logical progression. The rising incidence and prevalence of metabolic factors are increasingly becoming a global problem and we believe that this regional data will be potentially relevant to populations in other geographies too.

7. Limitations

This study, however, has a few limitations. The participating centers were not selected at random, but rather by the principal coordinating centre based on convenience, thereby contributing to a regional bias in case recruitment. However, given the large sample size in our investigation, this limitation may be considered minor. The control population could have been larger as planned but the COVID-19 outbreak seriously limited the recruitment of a healthy population. We are aware of the relevance of other risk variables like APO B, and LPA in the Indian population, however routine assessments of these are neither economically feasible nor logistically practical in routine patient care even in large tertiary institutes in India. Also, our study findings are limited to acute coronary syndrome in a hospital setting and is not community based where there are reports of higher incidence of coronary artery disease and a probable difference in their risk factors.

- **What is already known**

  There is high prevalence of metabolic factors in Indian population and presence of metabolic factors increase risk of acute coronary syndrome.

- **What this study adds**

  The results demonstrate that specific metabolic risk factors confer a similar risk as conventional risk factors.Primary prevention of ACS is optimal when both specific metabolic and conventional risk factors are addressed for assessment and intervention.

Having said that, the strength of our study is that we chose criteria that could be used across the country on a routine basis and whose modification would have an impact on acute coronary syndrome prevention.

8. Conclusion

There is a high proportion of metabolic risk factors in acute coronary syndrome patients in India. The risk of acute coronary syndrome conferred by specific metabolic risk factors (High waist: hip ratio, low HDL-C and high HbA1c) is comparable to that caused by conventional risk factors. Focusing on these MRF in addition to the CRFs for screening general population is likely to have an impact in minimizing the incidence of ACS in India.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2022.07.002.

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