

Detection of High-Risk Pathogenic Alleles for Young-Onset Myocardial Infarction in a Malaysian Cohort: A Pilot Study

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ABSTRACT

INTRODUCTION: Identifying pathogenic genetic variants associated with young-onset myocardial infarction (YOMI) may facilitate early risk stratification and enable timely preventive intervention. This pilot study aimed to compare the genetic profiles of patients with YOMI with healthy controls to identify high-risk genetic variants and evaluate the utility of polygenic risk scores (PRS) in differentiating genetic susceptibility between the two groups.

MATERIALS AND METHODS: Genomic DNA was extracted from patients with YOMI (n=30; mean age = 37.47 ± 3.29 years) and healthy controls (n=12; mean age = 34.67 ± 2.71 years). Samples were genotyped using the Asian Screening Array (Infinium®, Illumina). Genetic variants associated with cardiovascular risk were identified through annotation against the Genome-Wide Association Studies (GWAS) database. Polygenic risk scores were calculated and compared between the two groups. **RESULTS:** Thirty-seven single nucleotide polymorphisms (SNPs) with odds ratios greater than 2 were identified, including variants associated with coronary heart disease, venous thromboembolism, and atrial fibrillation. The rs13082914 variant in *KCNAB1* showed a strong association with young-onset myocardial infarction (OR=8.63; P<0.05). Polygenic risk score analysis revealed higher risk loads in YOMI patients for Brugada syndrome, myocardial infarction in CAD, peripheral artery disease, and non-BMP2 pulmonary arterial hypertension.

CONCLUSION: This pilot study demonstrated the potential value of genetic screening to identify individuals at risk of developing YOMI. However, larger prospective studies are required to validate these findings and to determine their clinical utility in risk prediction and preventive cardiovascular care.

Keywords

pathogenic alleles, young, myocardial infarction

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INTRODUCTION

Cardiovascular disease remains the leading cause of death worldwide, with mortality increasing from 12.1 million in 1990 to 18.6 million in 2019.¹ The World Health Organization (WHO) estimated that 17.6 million

people died from cardiovascular disease in 2016, with most of these deaths (80%) occurring in low- and middle-income countries.² In Malaysia, the average age of patients with cardiovascular disease is 58.5 years, which is younger than in neighbouring countries such

as Singapore (68.3 to 69.2 years) and Thailand (63.5 years).³ Risk factors for cardiovascular diseases include high blood pressure, sex, age, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor diet, and excessive alcohol consumption.⁴ It is estimated that more than 30% of elderly Malaysians are obese and also have hypertension and diabetes.⁵ Most cardiovascular diseases are preventable. Preventive measures to reduce cardiovascular risk include adopting a healthy lifestyle, such as maintaining a balanced diet, engaging in regular physical activity, and undergoing routine cardiovascular health assessments.⁶

With the advent of precision medicine, where medical treatment is personalised to the individual rather than the entire population, screening for high-risk alleles that contribute to cardiovascular diseases becomes essential. Genome-wide association studies (GWAS) have provided significant insights into the link between high-risk alleles and cardiovascular conditions, including incident myocardial infarction, coronary artery disease, atrial fibrillation, and reduced left ventricular function.^{7,8} Mapping single-nucleotide polymorphisms (SNPs) with the genotype-phenotype database of GWAS helps in identifying risk alleles associated with disease development and ultimately aids in developing prevention strategies for high-risk individuals.⁹ Developed countries have adopted GWAS, mainly among those of European ancestry, to identify SNPs linked to cardiovascular diseases.¹⁰ However, populations from developing countries remain underrepresented in GWAS, and significant disease associations observed in populations from developed nations might not apply to those in developing countries.

Given the significant economic and health impact of cardiovascular diseases, screening for high-risk alleles associated with these conditions is crucial for prevention. Furthermore, many individuals in Malaysia face a risk of developing cardiovascular diseases due to the widespread presence of risk factors within the country. Although these diseases predominantly

affect the elderly, there is a rising trend of young-onset myocardial infarction (YOMI) in Malaysia. Since the underlying mechanisms of YOMI remain unclear, we investigate the potential genetic predisposition of local patients with YOMI to identify predictive markers, aiming to facilitate the implementation of preventive medicine.

MATERIALS AND METHODS

Study population and sample collection

The study population included patients aged ≤ 40 years admitted to UiTM Medical Center (UMC) with myocardial infarction. Since there is no universal definition for young-onset myocardial infarction, we selected patients under 40 years old, as this age group represents an early presentation of the condition, consistent with previous studies.¹¹ Data on risk factors such as age, smoking status, diabetes mellitus, hypertension, and family history of myocardial infarction were collected from the patients. Whole blood samples were drawn from the patients and placed into EDTA tubes for SNP genotyping analysis. The genotype of the YOMI group was compared with that of the established healthy genome sequence database of Malaysians of the same age without cardiovascular diseases.

Sample processing (DNA extraction) and SNP analysis

DNA was extracted from blood samples using QIAamp® DNA Blood Mini Kits following the manufacturer's protocol (Qiagen Biotech Malaysia, Kuala Lumpur, Malaysia). For SNP genotyping analysis, DNA was prepared according to the Infinium Asia Screening Array protocol (Illumina, San Diego, CA, USA).

SNP calling, annotation, and the GWAS database

SNP or variant calling was performed using the GenomeStudio 2.0 software (Infinium Genotyping Data Analysis), and the identified SNPs or variants were annotated with traits related to cardiovascular diseases in the GWAS database. We obtained information,

including rsIDs, traits, risk alleles, and odds ratios (or Beta values) from the GWAS database. The polygenic risk score for individual patients was calculated using a previously published formula.¹²

Annotation of genetic variants associated with MI

We searched for genetic variants linked to myocardial infarction (MI) using the GWAS database. All cardiovascular-related variants from the GWAS database, that is, 31 traits and 878 SNPs, were successfully retrieved. After removing duplicates and unrelated traits, 391 SNPs and 31 traits remained. We further excluded non-related SNPs and traits in subsequent analyses. Ultimately, 19 cardiovascular-related traits and 316 SNPs were selected for further analysis to assess the significance of the risk alleles for myocardial infarction. The odds ratio/beta values, as well as the polygenic risk scores, were calculated for the pathogenic alleles.

Statistical analysis

The association between genotypes and the risk of myocardial infarction was analysed using Fisher's exact test. The odds ratio was calculated with a 95% confidence interval. A p-value of 0.05 was regarded as significant. All analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS) version 22.

Bioinformatics analysis

PredictSNP1 and PredictSNP2 were used to predict the pathogenicity of SNPs sourced from the GWAS database.^{13,14} PredictSNP1 evaluates the pathogenicity of protein mutations using eight established bioinformatics tools available for this purpose: 1) SIFT, 2) PANTHER, 3) MAPP, 4) PhD-SNP, 5) PolyPhen-1, 6) PolyPhen-2, 7) SNAP, and 8) MAPP. After assessing the performance of these tools, only the six best-performing ones were selected for consensus prediction, with a confidence score ranging from 0 to 100. Pathogenicity was classified as 'deleterious' or 'neutral' based on the consensus from these top six tools.

The approach for Predictsnp1 was similar to that of Predictsnp2, although Predictsnp2 was specifically used for predicting the pathogenicity of disease-related nucleotide variants. It employed six established tools GWAVA, Funseq2, CADD, FATHMM, Fitcons, and DANN to generate a consensus regarding the pathogenicity of these variants.

As with Predictsnp1, the pathogenicity was categorised as 'deleterious' or 'neutral' with a confidence score between 0 and 100. The polygenic risk score (PRS) for patients and controls was calculated using the previously established formula.¹² The PRS scores for both groups were divided into percentiles: 1%, 1-5%, 5-10%, 10-20%, 20-40%, 40-60%, 60-80%, 80-90%, 90-95%, 95-99%, and 99-100%.

RESULTS

Patients' clinical characteristics

Thirty patients diagnosed with young-onset myocardial infarction were recruited for this study, while 12 healthy subjects served as controls. The average age of patients was 37.47 ± 3.29 years, whereas the average age of controls was 34.67 ± 2.71 years. The mean age at first diagnosis of myocardial infarction among the patients was 34.47 ± 3.01 years. The age of patients ranged from 27 to 40 years, with half of them ($n=15$) aged between 30 and 35, and 46.7% ($n=14$) aged between 36 and 40. One patient was 27 years old at the time of first diagnosis. The myocardial infarction subgroups included non-STEMI in 10 patients (33.3%) and STEMI in 19 patients (63.3%). Most patients were smokers ($n=16$; 53.3%), while eight (26.7%) were former smokers and four (13.3%) had no history of smoking. Dyslipidemia, hypertension, and diabetes mellitus were observed in 14 (46.7%), 13 (43.3%), and 7 (23.3%) patients, respectively. Two patients (6.7%) had a family history of cardiovascular diseases, while six (20%) had a history of myocardial infarction. Nearly all patients ($n=29$; 96.7%) had ischaemic heart disease. No patients had a history of peripheral vascular disease and chronic liver disease.

Table I: Patients' clinical characteristics

Clinical characteristics	Frequency, n (%)
Age first diagnosed with MI	
<30 years	1 (3.3)
30-35 years	15 (50.0)
36-40 years	14 (46.7)
Subgroups of MI	
Non-stemi	10 (33.3)
Stemi	19 (63.3)
USA	1 (3.3)
Smoking status	
Smoker	16 (53.3)
Former smoker	8 (26.7)
Never	6 (20.0)
Aspirin intake	
Yes	5 (16.7)
No	25 (83.3)
Dyslipidemia	
Yes	14 (46.7)
No	16 (53.3)
Hypertension	
Yes	13 (43.3)
No	17 (56.6)
Diabetes mellitus status	
Yes	7 (23.3)
No	23 (76.7)
Insulin dependency	
Yes	1 (3.3)
No	29 (96.7)
Pharmacogenomics-guided treatment	
Yes	2 (6.7)
No	28 (93.3)
Family history of CVD	
Yes	2 (6.7)
No	28 (93.3)
History of MI	
Yes	6 (20)
No	24 (80)
Significant CAD	
Yes	4 (13.3)
No	26 (86.7)
New onset angina	
Yes	17 (56.7)
No	13 (43.3)
Chronic angina	
Yes	5 (16.7)
No	25 (83.3)
History of fractured neck of femor	
Yes	2 (6.7)
No	28 (93.3)
Cerebrovascular accident	
Yes	2 (6.7)
No	28 (93.3)
Chronic kidney disease	
Yes	2 (6.7)
No	28 (93.3)
Ischemic heart disease	
Yes	29 (96.7)
No	1 (3.3)

Abbreviations; MI:myocardial infarction; CVD: cardiovascular disease; CAD: coronary artery disease

Association of selected SNPs with myocardial infarction

Table I shows baseline characteristics of patients included in the study. Table II displays the association

of selected SNPs with myocardial infarction traits in 30 patients and 12 controls. Thirty-seven (37) SNPs were linked to myocardial infarction ($OR > 2$). The traits with the highest number of SNPs identified in the YOMI cohort were related to coronary heart disease (14 SNPs), followed by venous thromboembolism (10 SNPs), and atrial fibrillation (nine SNPs). Notably, the SNP rs13082914, located in the gene *KCNAB1*, was significantly associated with young myocardial infarction ($OR: 8.63$; $P < 0.05$).

Polygenic risk score (PRS) and patient risk

PRS scores for 20 myocardial traits were calculated for cases and controls. The PRS scores are shown in Table III. Scores for traits linked to Brugada syndrome, myocardial infarction in coronary artery disease, peripheral artery disease, and pulmonary arterial hypertension (without *BMPR2* mutations) were higher in cases than in the control group. Conversely, PRS scores for traits associated with atrial fibrillation, Behcet's disease, coronary heart disease, hypertension, intracranial aneurysm, ischemic stroke (cardioembolic and large artery atherosclerosis), large artery stroke, myocardial infarction (early onset), stroke, and sudden cardiac arrest were higher in controls than in cases.

SNP pathogenicity in myocardial infarction

We evaluated SNPs for pathogenicity, their genomic locations, mutation types, and confidence scores of pathogenicity using PredictSNP2. Out of the 37 SNPs examined, only two were predicted to be harmful, while the remaining were deemed neutral. The two SNPs predicted to be deleterious included rs11057401 (T>A: missense variant situated in the *CCDC92* gene, which is involved in DNA repair) and rs2296610 (G>T: missense variant located in the *NEBL* gene that encodes nebulin protein in cardiac muscle), with confidence scores of 82% and 89%, respectively.

Table II: List of high risk SNPs associated with young myocardial infarction in Malaysian population

SNP	Trait	Gene	Risk allele	Odd ratio	95% CI	P-value
rs7025486	Abdominal aortic aneurysm	<i>DAB2IP</i>	A	1.831	0.472-7.104	0.499
rs9316871	Abdominal aortic aneurysm	<i>AL136962.1 - AL512484.1</i>	G	1.5	0.39-5.768	0.732
rs602633	Abdominal aortic aneurysm	<i>CELSR2 - PSRC1</i>	A	2.167	0.405-11.601	0.387
rs6516091	Abdominal aortic aneurysm	<i>AL118505.1 - FERMT1</i>	A	2.167	0.405-11.601	0.387
rs6843082	Atrial fibrillation	<i>LINC01438</i>	G	1.667	0.329-8.434	0.668
rs17042171	Atrial fibrillation	<i>PITX2 - LINC01438</i>	A	1.143	0.299-4.364	1
rs2106261	Atrial fibrillation	<i>ZFHX3</i>	A	1.429	0.361-5.656	0.726
rs17059534	Atrial fibrillation	<i>AC093849.2 - HAND2</i>	A	14.5	1.415-148.569	0.018
rs7164883	Atrial fibrillation	<i>HCN4</i>	G	4	0.443-36.145	0.247
rs883079	Atrial fibrillation	<i>TBX5</i>	A	4	0.443-36.145	0.247
rs3903239	Atrial fibrillation	<i>AL023495.1</i>	C	1.522	0.268-8.653	1
rs76097649	Atrial fibrillation	<i>KCNJ5</i>	A	1.3	0.205-8.247	1
rs639652	Atrial fibrillation	<i>AL023495.1</i>	C	1.522	0.268-8.653	1
rs10821415	Atrial fibrillation	<i>AOPEP</i>	A	4	0.967-16.551	0.084
rs12044963	Atrial fibrillation	<i>KCND3</i>	T	1.234	0.314-4.840	1
rs10458660	Atrial fibrillation	<i>LRMDA</i>	G	1.375	0.323-5.847	0.715
rs7687819	Atrial fibrillation	<i>ALPK1</i>	A	1.692	0.169-16.912	1
rs133902	Atrial fibrillation	<i>MYO18B</i>	T	1.273	0.105-15.501	1
rs7616215	Behcet's disease	<i>CCR3</i>	C	1.643	0.378-7.134	0.699
rs7574070	Behcet's disease	<i>STAT4</i>	A	2.750	0.295-25.678	0.651
rs671	Coronary artery disease	<i>ALDH2</i>	A	4.667	0.67-32.488	0.131
rs1878406	Coronary artery disease	<i>PRMT5P1 - EDNR4</i>	T	1.529	0.377-6.207	0.731
rs2681472	Coronary artery disease	<i>ATP2B1</i>	C	1.071	0.275-4.176	1
rs2281727	Coronary artery disease	<i>SMG6</i>	C	3	0.736-12.227	0.175
rs13232179	Coronary heart disease	<i>WDR86-AS1 - AC005996.1</i>	A	5.5	0.62-48.817	0.133
rs11066280	Coronary heart disease	<i>HECTD4</i>	A	1.727	0.446-6.686	0.498
rs2123536	Coronary heart disease	<i>AC019055.1 - CISD1P1</i>	A	1.071	0.276-4.154	1
rs7808424	Coronary heart disease	<i>ASZ1, CFTR</i>	G	1.737	0.386-7.807	0.719
rs10933436	Coronary heart disease	<i>INPP5D, INPP5D</i>	A	2.895	0.534-15.689	0.282
rs4937126	Coronary heart disease	<i>ST3GAL4</i>	G	1.375	0.323-5.847	0.715
rs4387287	Hypertension	<i>STN1</i>	A	1.309	0.342-5.006	0.742
rs2398162	Hypertension	<i>NR2F2-AS1, AC012409.2</i>	A	1.818	0.325-10.157	0.696
rs11646213	Hypertension	<i>AC009117.2 - CDH13</i>	T	1.737	0.386-7.807	0.719
rs1735151	Hypertension	<i>IGSF5</i>	T	1.727	0.446-6.686	0.498
rs2066865	Venous thromboembolism	<i>FGA - FGG</i>	T	2	0.448-8.936	0.485
rs6088735	Venous thromboembolism	<i>EDEM2 - PROCR</i>	T	2.294	0.516-10.209	0.316
rs2296610	Atrial fibrillation	<i>NEBL</i>	T	3.3478	0.3654-30.6738	0.402
rs1152591	Atrial fibrillation	<i>ESR2, SYNE2</i>	T	2.1	0.5388- 8.1852	0.322
rs6882776	Atrial fibrillation	<i>NKX2-5 - AC008412.1</i>	G	2.5	0.5375-11.6274	0.405
rs242557	Atrial fibrillation	<i>MAPT</i>	G	3.4286	0.7662-15.3428	0.124
rs13082914	Coronary artery disease	<i>AC091607.2, KCNAB1</i>	T	8.6364	1.5934-46.8086	0.015
rs4773144	Coronary artery disease	<i>COL4A2</i>	G	2.3469	0.564- 9.7662	0.274
rs2244608	Coronary artery disease	<i>HNF1A, HNF1A-AS1</i>	C	3	0.7361- 12.2271	0.17465
rs12936587	Coronary heart disease	<i>AC020558.5 - SMCR2</i>	G	2.636	0.151-45.91	0.495
rs2505083	Coronary heart disease	<i>JCAD</i>	C	1.5294	0.3769-6.2067	0.731
rs4773144	Coronary heart disease	<i>COL4A2</i>	G	3.2857	0.7998- 13.4976	0.140519
rs7903146	Peripheral artery disease	<i>TCF7L2</i>	T	2.75	0.2945- 25.6795	0.65137
rs2217560	Pulmonary arterial hypertension (without <i>BMPR2</i> mutations)	<i>AC069114.1 - CBLN2</i>	G	2.75	0.2945- 25.6795	0.65137
rs687621	Venous thromboembolism	<i>ABO</i>	C	1.5	0.4077-5.5181	0.73755
rs7659024	Venous thromboembolism	<i>FGA - FGG</i>	A	2	0.4476-8.9363	0.48479
rs6536024	Venous thromboembolism	<i>FGG - LRAT</i>	C	2.333	0.59-9.2275	0.2919
rs2066865	Venous thromboembolism	<i>FGA-FGG</i>	T	2	0.4476-8.9363	0.4847986
rs8176749	Venous thromboembolism	<i>ABO</i>	A	2.1429	0.3886- 11.8154	0.46377
rs2066865	Venous thromboembolism	<i>FGA-FGG</i>	T	2	0.4476- 8.9363	0.484798
rs6088735	Venous thromboembolism	<i>EDEM2 - PROCR</i>	T	2.2941	0.5155- 10.2092	0.31631

Table III: Polygenic risk score (case vs control)

	Case	Control
Abdominal aortic aneurysm	34.53	34.755
Atrial fibrillation	40.767	41.763
Behcet's disease	16.51	18.42
Brugada syndrome	27.971	25.641
Coronary artery disease	25.69	25.855
Coronary heart disease	49.81	54.81
Hypertension	44.748	45.9
Intracranial aneurysm	84.58	86.64
Ischemic stroke (cardioembolic)	31.11	34.66
Ischemic stroke (large artery atherosclerosis)	0	4.17
Large artery stroke	39.11697	42.54
Myocardial infarction	63.89333	64.47833
Myocardial infarction (early onset)	50.331	52.5625
Myocardial infarction in coronary artery disease	38.33333	33.33333
Peripheral artery disease	21.755	20.25
Pulmonary arterial hypertension (without <i>BMPR2</i> mutations)	13.33333	4.166667
Stroke	4.918667	5.333333
Stroke (ischemic)	25.63333	27.25
Sudden cardiac arrest	8.333333	12.5
Venous thromboembolism	18.77315	17.05794

DISCUSSION

The prevalence of YOMI is higher in Malaysia than in developed countries. The main factors contributing to the increased risk of developing myocardial infarction are individual lifestyle and diet. In recent decades, as Malaysia has moved towards urbanisation and industrialisation, the lifestyles of young adults have become more unhealthy, characterised by increased consumption of fast foods and physical inactivity. This has led to a high prevalence of obesity among Malaysians. An unhealthy lifestyle combined with genetic susceptibility elevates the risk of myocardial infarction. Therefore, we carried out this study to investigate the genetic risks that increase susceptibility to YOMI in Malaysia. We also calculated the polygenic risk score for the cases and controls to examine the differences in genetic scores between the groups.

We extracted 316 SNPs from the GWAS database associated with cardiovascular diseases. Of these, 37 SNPs were identified in our study. These 37 SNPs were linked to myocardial infarction with an OR of over 2.

We also identified two SNPs predicted to be harmful using an online bioinformatics tool. These SNPs are involved in DNA repair and cardiac muscle development. We calculated PRS scores for patients and controls to predict the risk of MI based on the individual's genetics.

To the best of our knowledge, our study is the first to attempt to find an association between the risks of young myocardial infarction and PRS scores in our population. Although we observed certain myocardial infarction traits to be higher in cases than in controls, these findings were not statistically significant. This may be due to the small sample size of patients in our study. Additionally, we derived PRS scores based on the GWAS database, which predominantly includes participants of European descent. The GWAS database is underrepresented by Asian populations, with 80% of the subjects reported in the database being from Europe.¹⁵ Malaysia is a multicultural country with diverse ancestry, which may influence the distribution of risk alleles. The results of this study highlight the need to establish our own population genomic database for future research on genetic variants associated with disease. According to the American Heart Association, seven criteria must be met by young adults to prevent cardiovascular disease: 1) at least 150 minutes of moderate physical activity per week, 2) body mass index below 25 kg/m², 3) serum cholesterol under 200 mg/dl, 4) blood pressure of 120/80 mmHg, 5) fasting plasma glucose under 100 mg/dl, 6) a balanced diet low in fat, salt and sugar, and rich in vegetables and fruits, and 7) never smoking or quitting smoking for over a year.¹⁶ Results from our study identified high-risk alleles for young myocardial infarction, and the information obtained will be valuable for screening individuals at high risk of developing early-onset myocardial infarction for early intervention. Interestingly, the control groups exhibited higher PRS for MI (young onset), suggesting that they carry genetic risks for MI but may not express traits due to healthier lifestyles.

LIMITATION

The small sample size and single-centre design of the study may restrict the ability to generalise the results to a broader population. We recognize that our SNP selection was limited to variants annotated against the GWAS database, which predominantly represents individuals of European ancestry. This reliance may have excluded population-specific variants relevant to the Malaysian multiethnic cohort. As this is a pilot study, our aim was to evaluate feasibility using an established international database.

CONCLUSION

Although the sample size in our pilot study was small, we observed a higher prevalence of several genetic traits associated with myocardial infarction among patients with young-onset myocardial infarction (YOMI) than among healthy controls. These findings highlight the potential of genetic risk prediction for identifying YOMI within the Malaysian population. However, our genetic risk prediction was based on the Genome-Wide Association Studies (GWAS) database, which primarily derived from populations of European ancestry and may not fully capture the genetic architecture of Malaysians. Therefore, there is a need to establish population-specific genomic databases to improve the accuracy and clinical applicability of genetic risk prediction in Malaysia. Future multicentre studies with larger and more ethnically diverse cohorts are warranted to better characterize the genomic landscape of the Malaysian population and validate these preliminary findings.

Competency in medical knowledge

The prevalence of young-onset myocardial infarction is higher in Malaysia than in developed countries. Finding innovative ways to prevent and lessen the severity of the disease at its onset is crucial. This includes screening for high-risk alleles linked to cardiovascular diseases. The study identified thirty-seven (37) SNPs associated with myocardial infarction. Most SNPs found in patients with young-onset myocardial infarction were related to genetic traits of coronary artery disease,

thromboembolism, and atrial fibrillation. The SNP rs13082914 in the *KCNAB1* gene demonstrated a significant association with young-onset myocardial infarction, highlighting its potential role as a genetic marker for cardiovascular risk assessment.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare

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