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NON-TRADITIONAL RISK FACTOR ASSOCIATED WITH ACUTE CORONARY SYNDROME IN YOUNG AGE : A SYSTEMATIC REVIEW

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Abstract
In younger people all across the world, acute coronary syndrome remains one of the primary causes of death and disability. This is especially true in developing countries. Due to the fact that little reporting has taken place, there is a severe lack of data relevant to the patient group in question. Traditional risk factors, which are risk factors that have been well documented to increase the likelihood of developing acute coronary syndrome, such as smoking, hyperlipidemia, hypertension, a family history of atherosclerosis, a family history of obesity, and diabetes mellitus (DM), are becoming more prevalent in the younger population. In addition, illnesses that are typically uncommon among adults, including as obstructive sleep apnea (OSA), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), are more prevalent in younger patients with AMI. [Citation needed] Studies highlight the significant frequency and importance of established atherosclerotic risk factors such as smoking, hypertension, and a family history of coronary artery disease in addition to emerging risk factors such as systemic lupus erythematosus, obstructive sleep apnea, and HIV. These risk factors include smoking, hypertension, and a family history of coronary artery disease. In spite of the fact that we emphasize the significance of the non-traditional risk factors that were described earlier, it is essential to identify young patients who have traditional risk factors, and in particular those who have coexisting diseases such as HIV, OSA, and SLE, and to optimize their treatment in a way that takes these factors into account. In addition, we highlight the significance of the non-traditional risk factors that were described earlier.

Keyword: *Acute coronary syndrome; Risk Factor; Young Age*

INTRODUCTION

Acute coronary syndrome continues to be one of the leading causes of death and disability in younger people all over the world. There is a dearth of data pertaining to the patient population in question because inadequate reporting has occurred. Traditional risk factors, which are well documented risk factors for acute coronary syndrome, such as smoking, hyperlipidemia, hypertension, a family history of atherosclerosis, family history of obesity, and diabetes mellitus (DM), are becoming more widespread in the younger population.[1–3]

Because of factors such as greater lifespan, urbanization, and changes in lifestyle, the prevalence of acute coronary syndrome is rising in emerging countries. It is anticipated that the costs associated with acute coronary syndrome will rise from 47 million DALYs worldwide in 1990 to 82 million DALYs in 2020, with emerging nations accounting for sixty percent of this increase. Because of this, we are driven to discover a solution that will enhance the overall quality of patients' lives.[5,6]

Among addition, relatively infrequent diseases of adults, including as obstructive sleep apnea (OSA), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), are more prevalent in younger patients with AMI. There hasn't been a lot of research done on the unique risk variables using big national datasets.[1] This article investigate the association between non-traditional risk factor associated with acute coronary syndrome (ACS) in young age.

METHODS

Protocol

This systematic review adhered to the principles that were described in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist. These guidelines served as the foundation for the regulations that regulated the conduct of this systematic review.

Eligibility Criteria

This systematic review was developed to analyze papers on "non-traditional risk factor"; “acute coronary syndrome”; and "young age". These are the subjects that were covered in depth in the research that was taken into account. The following requirements have to be met in order for your work to be taken into consideration: 1) Articles have to be written in English. 2) Articles have to have been published after 2012, but before the time this systematic review is created. The following kinds of textual contributions will under no circumstances be considered for inclusion in the anthology: 1) Editorial letters, 2) contributions that do not have a Digital Object Identifier (DOI), and 3) article reviews and submissions that are comparable to those that have previously been published in the journal.

Search Strategy

The search for studies to be included in the systematic review was carried out from November 30th, 2022 using the PubMed and SagePub databases by inputting the words: "non-traditional risk factor"; “acute coronary syndrome”; and "young age". Where *"non-traditional"[All Fields] AND ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("risk"[All Fields] AND "factor"[All Fields]) OR "risk factor"[All Fields]) AND ("acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields] AND "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields]) AND ("young"[All Fields] OR "youngs"[All Fields]) AND ("agrosyst geosci environ"[Journal] OR "age"[Journal] OR "age omaha"[Journal] OR "age dordr"[Journal] OR "adv genet eng"[Journal] OR "age"[All Fields])* is used as search keywords.

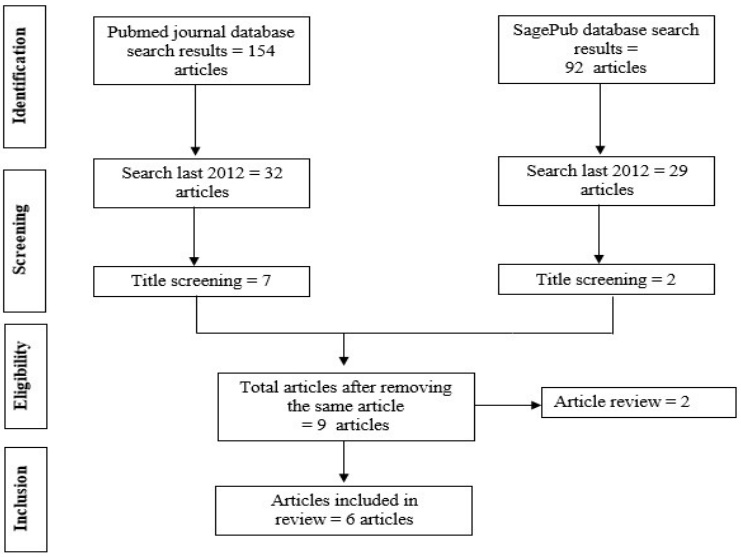

Figure 1. Article search flowchart

Data retrieval

After completing a literature analysis and reviewing the titles and abstracts of previously published research, the author of the study altered the criteria for what should and should not be included in the study. After reviewing previously published studies, the author made these adjustments. During the compilation of the systematic review, only those research projects that met each and every criterion were taken into account. This was done to guarantee that the review is as comprehensive as possible. It is possible to collect information about each individual study, including its title, author, publication date, study location of origin, research design, and research variables. This information can be provided in a variety of distinct formats.

Quality Assessment and Data Synthesis

The writers did their own independent reviews of a selection of the research listed in the titles and abstracts of the papers in order to decide which studies could be appropriate for consideration. After this step, the full texts of the studies that meet the criteria for inclusion in the systematic review will be read in order to determine which studies can be utilized as final inclusions for the purpose of the review. This will be done so that the question, "Which studies can we use for the review?" can be answered.

RESULT

First study by Krittanawong, et al (2020) showed Human immunodeficiency virus (HIV), systemic lupus erythematosus (SLE), and obstructive sleep apnea (OSA) were associated with a higher risk of developing an acute myocardial infarction (AMI) in the young after multivariable analyses were adjusted for age, sex, race, family history of atherosclerosis, body mass index (BMI), diabetes, hypertension, hyperlipidemia, chronic kidney disease Rheumatoid arthritis was connected to a reduced risk of AMI (adjusted OR = 0.83; 95% confidence interval [CI]: 0.76–0.89, p <0.001). Smoking cigarettes (adjusted odds ratio [aOR] = 1.98; 95% CI = 1.95–2.02, p <0.001), obesity (aOR = 1.37; 95% CI = 1.33–1.41, p = 0.003), hyperlipidemia (aOR = 1.07; 95% CI = 1.04–1.08, p <0.001), and family history of coronary artery disease (CAD) (aOR = 1.35; 95% CI = 1.3–1.4, p <0.001) were also associated with a higher risk of developing an AMI in the young.[4]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size / Characteristic	Risk Factor	Result
Krittanawong, 2020[4]	United State (US)	Retrospective study	5,764,755 hospitalized young individuals (<55 years)	SLE, HIV and OSA	After multivariable analyses adjusted for age, sex, race, family history of atherosclerosis, body mass index (BMI), diabetes, hypertension, hyperlipidemia, chronic kidney disease, and current cigarette smoking, novel risk factors like HIV, SLE, and OSA were associated with a higher risk of AMI in the young (adjusted OR for HIV = 4.06; 95% CI = 3.48–4.71, p <0.001). Rheumatoid arthritis reduced AMI risk (aOR = 0.83; 95% CI = 0.76–0.89, p <0.001). After multivariable analyses, cigarette smoking, obesity, hyperlipidemia, and a family history of CAD were also associated with a higher risk of young AMIs.
Freiberg, 2013[5]	United State	Prospective longitudinal cohort	82,459 participants	HIV	871 AMI events occurred over 5.9 years. HIV-positive veterans had significantly more AMI events per 1000 person-years than uninfected veterans across three decades of age: 2.0 (1.6-2.4) vs 1.5 (1.3-1.7); 3.9 (3.3-4.5) vs 2.2 (1.9-2.5); and 5.0 (3.8-6.7) vs 3.3 (2.6-4.2) (P <0.05). HIV-positive veterans had a higher risk of incident AMI than uninfected veterans (HR = 1.48; 95% CI= 1.27-1.72). An excess risk remained among those achieving an HIV-1 RNA level less than 500 copies/mL compared with uninfected veterans in time-updated analyses (HR = 1.39; 95% CI = 1.17-1.66).
Drozd, 2017[6]	US	Retrospective study	29,169 HIV-infected individuals	HIV	IR for T1MIs was 2.57[2.30–2.86] per 1000 person-years, and the aIRR was significantly higher compared with participants in ARIC (1.30[1.09–1.56]). In multivariable analysis restricted to HIV-infected individuals and including traditional CVD risk factors, the rate of T1MI increased with decreasing CD4 count (≥500 cells/μL: ref; 350–499 cells/μL: aIRR=1.32[0.98–1.77]; 200–349 cells/μL: aIRR=1.37[1.01–1.86]; 100–199 cells/μL: aIRR=1.60[1.09–2.34]; <100 cells/μL: aIRR=2.19[1.44–3.33]). Risk associated with detectable HIV RNA (<400 copies/mL: ref; ≥400 copies/mL: aIRR=1.36 [1.06–1.75]) was significantly increased only when CD4 was excluded.
Avina-Zubieta, 2017[7]	United Kingdom	Retrospective study	4,863 individuals with SLE	SLE	SLE patients had fully adjusted multivariable HRs of 2.61 for MI, 2.14 for stroke, and 2.28 for CVD compared to non-SLE persons. The age-, sex-, and entry time–matched HRs for MI, stroke, and CVD were highest in the first year following SLE diagnosis: 5.63 (95% CI = 4.02–7.87), 6.47 (4.42–9.47), and 6.28 (4.83–8.17).
Chen. 2018[8]	Taiwan	Retrospective study	52,840 subjects	RA	RA was associated with a higher risk of cardiovascular disease and coronary artery disease in young individuals, particularly in those who were at risk of ischemic stroke (HR = 3.48; 95% CI = 2.16–5.61). Participants diagnosed with RA had a 2.35-fold increased risk of cardiovascular disease and coronary artery disease in comparison to patients who did not have RA at the start of the study. The risk of cardiovascular disease and coronary artery disease was increased when RA was combined with hypertension. Patients diagnosed with RA and hypertension had a higher risk of cardiovascular disease and coronary artery disease (HR = 9.08; 95% CI = 7.22–11.41) as compared to participants who did not have RA and hypertension.
Hansen, 2019[9]	Denmark	Retrospective study	788 patients with RA and 1,641 controls	RA	Patients with RA had significantly increased risk of CAD (RR = 1.26 [95% CI 1.04–1.52]; p = .021) and increased weighted mean differences for CCS (48.25 [95% CI 26.97–69.53]; p < .001) compared to controls. Limited evidence suggested that patients with RA had a higher prevalence of moderate-severe (CCS > 100) CAD and more multivessel CAD, and RA duration and disease activity were associated with higher CCS, RA disease activity was linked with presence of high risk (non-calcified or mixed) coronary plaques, and treatment with methotrexate was tied to absence of CAD, respectively.

There were 871 cases of AMI over the course of a follow-up period that averaged 5.9 years. The mean (95% CI) number of AMI events per 1000 person-years was consistently and significantly higher for HIV-positive veterans compared with

uninfected veterans across three decades of age: for those aged 40-49 years, 2.0 (1.6-2.4) vs 1.5 (1.3-1.7); for those aged 50-59 years, 3.9 (3.3-4.5) vs 2.2 (1.9-2.5); and for those aged 60 to 69 years, 5.0 (3.8-6.7) vs 3.3 In HIV-positive veterans, the risk of incident acute myocardial infarction (HR = 1.48; 95% CI = 1.27-1.72) was significantly higher than in HIV-negative veterans, even after adjusting for Framingham risk factors, comorbidities, and substance use. In time-updated analyses, there was still an increased risk among those who had achieved an HIV-1 RNA level of less than 500 copies/mL in comparison with uninfected veterans (HR = 1.39; 95% CI = 1.17-1.66).[5]

IR for T1MIs was 2.57 [2.30–2.86] per 1000 person-years, and the aIRR was significantly higher compared with participants in ARIC (1.30[1.09–1.56]). In multivariable analysis restricted to HIV-infected individuals and including traditional CVD risk factors, the rate of T1MI increased with decreasing CD4 count (≥500 cells/μL: ref; 350–499 cells/μL: aIRR=1.32[0.98–1.77]; 200–349 cells/μL: aIRR=1.37[1.01–1.86]; 100–199 cells/μL: aIRR=1.60[1.09–2.34]; <100 cells/μL: aIRR=2.19[1.44–3.33]). Risk associated with detectable HIV RNA (<400 copies/mL: ref; ≥400 copies/mL: aIRR=1.36 [1.06–1.75]) was significantly increased only when CD4 was excluded.[6]

In SLE patients, the fully adjusted multivariable HRs for heart attack were 2.61 (95% CI = 2.12–3.20), for stroke they were 2.14 (95% CI = 1.64–2.79), and for cardiovascular disease they were 2.28 (95% CI = 1.90–2.73). These findings were compared to individuals who did not have SLE. The age-, sex-, and entry time–matched HRs for heart attack, stroke, and cardiovascular disease were at their highest during the first year after a diagnosis of SLE. These HRs were as follows: 5.63 (95% CI = 4.02–7.87), 6.47 (95% CI = 4.42–9.47), and 6.28 (95% CI = 4.83–8.17), respectively.[7]

RA was associated with a higher risk of cardiovascular disease and coronary artery disease in young individuals, particularly in those who were at risk of ischemic stroke (HR = 3.48; 95% CI = 2.16–5.61). Participants diagnosed with RA had a 2.35-fold increased risk of cardiovascular disease and coronary artery disease in comparison to patients who did not have RA at the start of the study. The risk of cardiovascular disease and coronary artery disease was increased when RA was combined with hypertension. Patients diagnosed with RA and hypertension had a higher risk of cardiovascular disease and coronary artery disease (HR = 9.08; 95% CI = 7.22–11.41) as compared to participants who did not have RA and hypertension.[8]

Patients with RA had significantly increased risk of CAD (RR = 1.26 [95% CI 1.04–1.52]; p = .021) and increased weighted mean differences for CCS (48.25 [95% CI 26.97–69.53]; p < .001) compared to controls. Limited evidence suggested that patients with RA had a higher prevalence of moderate-severe (CCS > 100) CAD and more multivessel CAD, and RA duration and disease activity were associated with higher CCS, RA disease activity was linked with presence of high risk (non-calcified or mixed) coronary plaques, and treatment with methotrexate was tied to absence of CAD, respectively.[9]

DISCUSSION

Patients who have HIV have been shown to have an increased risk of MI, when adjusted for risk, according to large population studies. Patients with HIV have also been shown to have a risk of MI that is at least 1.5 times higher, according to several studies. The findings of our research are consistent with this finding as well. In point of fact, a low CD4 count as well as elevated levels of HIV RNA in the plasma have both been linked to an increased risk of premature MI. This risk appears to be independent of both the negative metabolic effects of antiretroviral therapy and the traditional risk factors for atherosclerosis.[5,6,10]

Chronic inflammation caused by HIV infection, immune activation as a result of HIV infection, and ensuing endothelial dysfunction are some of the mechanisms that have been hypothesized to be responsible for the increased risk of premature MI. The Veterans Aging Cohort Study Virtual Cohort found that HIV infection may increase MI risk like diabetes. HIV infection may be a risk factor for myocardial infarction in young people, like hypertension and smoking. Therefore, aggressive measures targeting primary prevention of ischemic heart disease should be considered in these individuals in addition to optimizing HIV infection.[5,6,10,11]

SLE is a heterogeneous autoimmune illness, and it has a well-established relationship with endothelial dysfunction and systematic inflammation in various organs, which promotes accelerated atherosclerosis. This is due to the fact that SLE is a heterogeneous disease. Among the common comorbidities associated with SLE is myocardial infarction (MI), which may be reported in as many as 16% of SLE patients. Patients with SLE may be predisposed to MI via a mechanism of coronary artery thrombosis or embolization, or coronary arteritis. This may occur even in the absence of coronary atherosclerosis on coronary angiography.[12,13] Patients diagnosed with SLE had a greater adjusted risk of MI, according to a number of studies, which compared them to controls who did not have SLE.[7]

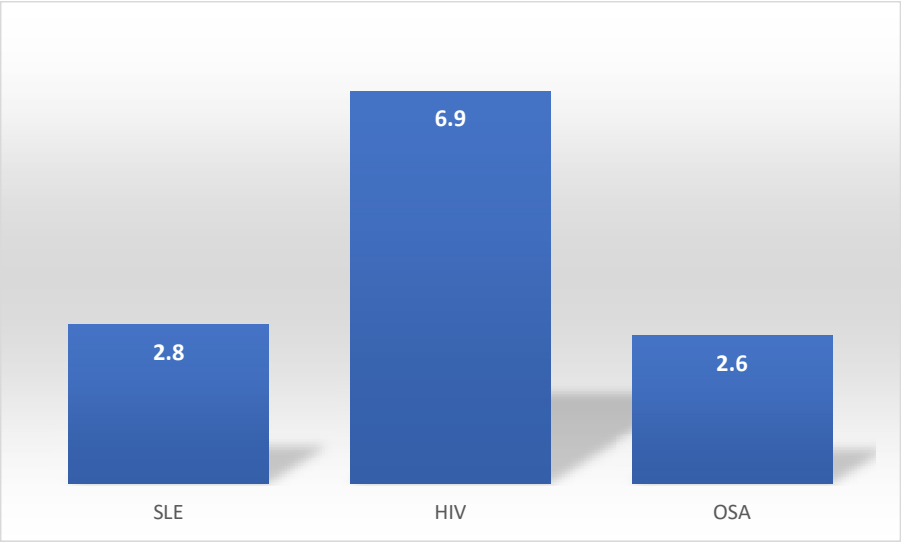

Figure 2. Comparison of the occurrence of ACS based on non-traditional risk factors

In the Nurses' Health Study of 119,332, which primarily consisted of Caucasian women and had a follow-up period of 28 years, the presence of SLE was associated with a 2-fold increased risk of cardiovascular end points, including fatal and nonfatal MI (2.26; 95% CI 1.45 to 3.52, p = 0.001). The study included a follow-up duration of 28 years, and the average age of participants when they were diagnosed with SLE was 53 years old. In spite of the absence of traditional atherosclerotic risk factors, the findings from our analyses are consistent with the findings from the studies that were mentioned previously. Furthermore, these findings provide evidence from a nationwide scale to suggest that patients with SLE should be considered to be at an elevated risk for premature MI.[4,14]

Research has shown that RA is a separate risk factor for MI in young adults. A recent meta-analysis found that individuals with RA had a significantly elevated risk of coronary artery disease (RR = 1.26 [95% CI 1.04–1.52]; p = 0.021) when compared to controls. After taking established atherosclerotic risk factors into account, our research showed, intriguingly, that patients with RA had a decreased likelihood of experiencing a myocardial infarction (MI).[8,15] In spite of the fact that these findings go counter to what the conclusions of previous analyses have shown, we have a strong suspicion that there are other causes underlying our contradictory findings.[9,16]

To begin, the average age at which individuals are diagnosed with RA ranges between the fifth and sixth decades of their lives.[16] It has been shown that patients who are diagnosed with young onset rheumatoid arthritis have lower disease activity than these patients, which may explain why young patients with RA in our cohort had a lower likelihood of MI.[17,18] Patients who are diagnosed with young onset rheumatoid arthritis have been shown to have lower disease activity. In addition, the processes that are thought to be behind AMI in patients who have RA include vascular dysfunction and plaque instability as a result of a chronic inflammatory state.[19]

It has been proven that the length of time a patient has had their disease is an independent risk factor for developing cardiovascular disease.[20] As a result, we have a hunch that the young patients in our cohort may have had an overall shorter disease duration (due to the fact that they were younger), which may have contributed to a lower likelihood of AMI. Lastly, taking into account the database of inpatient hospital admissions from all over the country, we have a sneaking suspicion that some of the patients who were included in our research were already receiving optimal treatment with anti-rheumatic medications such as ASA or disease-modifying antirheumatic drugs (DMARDs).[21]

However, the doses of aspirin recommended for the prevention of coronary artery disease are significantly lower than those recommended for the treatment of rheumatoid arthritis. There is evidence to suggest that treatment with DMARDs can lower the chance of developing cardiovascular disease. DMARDs are implicated in anti-cytokine activities such as the suppression of tumor necrosis factor alpha, interleukin-6 (IL-6), and interleukin-1 (IL-1).[21] The usage of DMARDs was shown in a case control research to have the ability to reduce inflammation, which in turn led to a lower risk of developing atherosclerosis.[22]

There is a significant incidence of obstructive sleep apnea that has not been detected in patients who have been hospitalized with a MI, and up to 42 percent of patients who have been hospitalized with a STEMI have severe obstructive sleep apnea that has not been diagnosed.[23,24] The independent association between OSA and MI has been well recognized, and it has been attributed to the oxidative stress that is caused by reactive oxygen species, which in turn causes coronary microvascular injury and endothelial injury.[25]

This association was initially the subject of conflicting data, but it has since been cleared up. OSA was revealed to be an independent predictor of the risk of recurrent MI in one study, while another study came to the conclusion that OSA raises the risk of MI regardless of traditional atherosclerotic risk factors.[26] The findings of our analysis are consistent with those of previous research and provide light on the significance of OSA in young patients who are at an increased risk of greater accumulated lifetime risk for cardiovascular comorbidities as a result of AMI.[27]

Studies highlight the significant frequency and importance of established atherosclerotic risk factors such as smoking, hypertension, and a family history of coronary artery disease in addition to emerging risk factors such as systemic lupus

erythematosus, obstructive sleep apnea, and HIV. In spite of the fact that we highlight the significance of the non-traditional risk factors described earlier, it is essential to identify young patients who have traditional risk factors, and in particular those who have coexisting diseases such as HIV, OSA, and SLE, and to optimize their treatment in a way that takes these factors into account.

CONCLUSION

In spite of the fact that we emphasize the significance of the non-traditional risk factors that were described earlier, it is essential to identify young patients who have traditional risk factors, and in particular those who have coexisting diseases such as HIV, OSA, and SLE, and to optimize their treatment in a way that takes these factors into account. In addition, we highlight the significance of the non-traditional risk factors that were described earlier.

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