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Original Article

Association between Factor-V Leiden and occurrence of acute myocardial infarction using a large NIS database

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Abstract: Factor V Leiden is an inheritable pro-thrombotic genetic condition caused by a point mutation at the 506th codon, resulting in activated protein C resistance. APC resistance has been shown to contribute to the development of venous thrombosis. However, the role of FVL in AMI has yet to be well defined in the current literature. To assess whether a mutation carrier is more apt to develop an AMI, we conducted a retrospective observational analysis of two populations aged 18-40 and 18 through end of life. We used ICD-10 codes to search the NIS, an electronic nationwide patient database, to establish our populations and obtain our data. The ICD-10 codes were specific for activated protein C resistance and acute myocardial infarction. Preliminary data indicated that FVL was related to AMI; however, this finding became insignificant in both populations when stratified for age. We concluded there was no association between Factor V Leiden and acute myocardial infarction across both examined populations. Future investigations into this field of research are warranted as there remains a need for more consensus among the scientific community. Background: Medical literature regarding the correlation between Factor V Leiden (FVL) and acute myocardial infarctions (AMI) is controversial. We aim to investigate the association between FVL and AMI. Materials and Methods: Using the Nationwide Inpatient Sample database, we evaluated any association between Factor V Leiden and acute myocardial infarction in 2016 using ICD-10 codes. Results: Univariate analysis (18-40) showed an increase of AMI in patients with FVL 0.6% vs. 0.4%. However, after adjustment for age and comorbid conditions in multivariate analysis, FVL was not significantly associated with acute myocardial infarction (OR 1.44 (95% CI 0.913-2.273, *p*-value 0.117)). Univariate analysis (all patients over 18 years old) found that 2.9% of patients with FVL experienced AMI vs. 4.4% without the mutation. Multivariate analysis of the entire population ultimately showed no correlation between FVL and AMI. Conclusion: In a population over 18, Factor V Leiden did not correlate with an increased risk of acute myocardial infarction in our studied population.

Keywords: Factor V Leiden, FVL, myocardial infarction, MI, primary hypercoagulable state, deep venous thrombosis, activated protein C resistance

Introduction

Factor V, an essential procoagulant protein produced by the liver, plays a significant role in blood coagulation and hemostasis [1-3]. The typical sequence of thrombosis and hemostasis includes the sequential activation and deactivation of a series of clotting factors following an injury to tissue or the vasculature [4]. These injury pathways culminate with activated Factor V promoting thrombin and clot formation. Once the appropriate degree of clot formation has developed, activated protein C (APC) will inhibit Factor V, thus returning the body to normal homeostasis. Factor V Leiden, present in 3-8% of European Caucasians, is the most common genetic etiology of inherited hypercoagulability affecting this clotting cascade. A myocardial infarction, by contrast, "usually develops as a result of thrombosis originating from a ruptured atherosclerotic plaque in one of the coronary arteries" [11].

FVL is caused by a gain-of-function point mutation exchanging guanine for adenine at the 506th codon, causing the amino acid arginine to be replaced by glutamine [1, 5, 6]. This mutation results in activated Factor V resistant to

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cleavage by activated protein C, thus encouraging a hypercoagulable state [1-4]. Inheritance of this hypercoagulable state is a known risk factor for developing venous thrombus and thromboemboli [2, 5-10]. The inheritance pattern of the mutation also determines the degree of risk, with heterozygosity accounting for 3-8 times increased risk of venous blood clots, and homozygous inheritance demonstrates up to an 80 times increased risk profile [1]. There is a well-established and clinically significant link between FVL and venous thromboemboli in the medical literature. Interestingly, there is significantly less information examining the association between FVL and acute myocardial infarction (AMI) [10, 12-14].

The current data has yet to reach a consensus on the influence of Factor V Leiden on acute myocardial infarctions due to various factors, including the geographic distribution of FVL, variable study designs, and small sample sizes [5, 15-18]. For example, a Moroccan study in 2016 found that FVL was not a predisposing factor to myocardial infarctions because the frequency of the FVL mutation in the study population was practically zero [19]. Conversely, similar studies in Egypt and North India indicated that FVL was associated with an increased risk of AMI [17, 20]. Meta-analysis and large-scale studies have faced the dilemma of failing to reach a universal consensus, partially due to the difficulty in reproducing genetic studies and the diversity of data aggregated for each meta-analysis. A meta-analysis in Circulation [24] recognized that FVL is not a risk factor for subsequent MI. In contrast, meta-analyses published by the Lancet in 2006 [21], Genetic Testing and Molecular Biomarkers [22], and the American Heart Journal in 2003 [23] concluded that FVL may be a risk factor for AMI. Meanwhile, the Copenhagen Heart Study [25] and the Physician's Health Study [6] found that FVL is not associated with an increased risk of AMI. Our study aimed to investigate the possible association between FVL and AMI using a National database and ICD-10 codes for 2016 via a retrospective observation analysis.

Methods

Data collection

We conducted a retrospective review utilizing the National Inpatient Sample (NIS). The NIS is a collection of hospital inpatient databases from the Healthcare Cost and Utilization Project (HCUP). The NIS was designed for trending national healthcare utilization, quality of healthcare, and patient outcomes. Part of its' design is to maintain a database of patient demographics and their reasons for hospitalization via ICD-10 billing codes. By searching for specific ICD-10 codes, we extracted patient demographics relevant to our study from each associated billing code. We then built our statistical model and drew comparative data from this pool. The NIS database is available at www.hcup-us.ahrq.gov.

We utilized the NIS database to collect the data for our analysis. First, we determined the total population of individuals aged 18-40 who were seen at NIS-affiliated hospitals in 2016. We then narrowed the parameters of our search using the International Classification of Diseases, tenth revision, and Modification (ICD-10-CM) codes D68.51 (activated protein C resistance) and I21, I22, I23, and I24 (acute myocardial infarctions) to determine the number of individuals in this population group who carried the diagnosis of activated protein C resistance or acute myocardial infarction. This population was subjected to a univariate analysis to determine the prevalence of AMI in the FVL and the non-FVL populations. A multivariate analysis of individuals positive for FVL was then conducted with and without age adjustment. A second series of searches utilizing the same parameters and ICD-10 codes was performed without the 40-year age restriction. This newly expanded population was subjected to the same univariate and multivariate analysis as the 18-40 age group. The multivariate analysis of both demographics included accounting for diabetes, hypertension, hyperlipidemia, race, and gender. Inclusion into our study was purposefully broad to avoid a selection bias. Still, it was limited to individuals admitted to NIS hospitals in 2016 and those who carried the specific ICD-10 codes of interest: D68.51, I21, I22, I23, and I24. The four acute myocardial infarction codes were grouped during the data analysis. Patients under 18 were excluded from the study, and the 40-year age cut-off separated the two database searches.

Statistical analysis

Retrospective univariate and multiple regression analyses on the NIS data adjusted for

Table 1. Univariate analysis of patients under 40 with and without Factor V Leiden and myocardial infarction in 2016

	FVL positive		FVL negative	
	FVL & AMI	FVL & No AMI	No FVL & AMI	No FVL & No AMI
Total	19	3134	5542	1522977
Percent	0.6%	99.4%	0.4%	99.6%

0.4% of the total population experienced an AMI. Total population = 1,531,672. FVL: Factor V Leiden. AMI: Acute Myocardial Infarction.

Table 2. Multivariate analysis, without age adjustment, of patients with FVL in 2016

	P-value	OR	95% CI for OR	
			Lower	Upper
MI	0.04	1.63	1.03	2.57
Diabetes	0.02	1.24	1.04	1.49
Hypertension	<0.01	1.60	1.42	1.80
Hyperlipidemia	0.29	1.26	0.82	1.92
Race (white)	<0.01	4.29	3.92	4.69
Gender (female)	<0.01	1.73	1.58	1.91
Constant	0.03	4.07		

comorbid conditions in the multivariate analysis will be reported as means, Confidence Interval's for continuous variables and frequencies, and proportions for categorical variables. Chi-squared/Fisher's Exact test will be used to compare categorical variables. For categorical/binary outcomes, multiple logistic regression will be used to ascertain the likelihood of the outcome (Odds Ratios (95% CI)) occurring between the characteristics. All statistical models will be adjusted for confounding. All analyses will be conducted following the implementation of population discharge weights. All *p*-values will be 2-sided and P<0.05 will be considered statistically significant. Data will be analyzed using STATA 17 (Stata Corporation, College Station, TX).

Results

The first NIS search yielded 1,531,672 individuals aged 18-40. Of these individuals, 3,153 carried the FVL mutation, and 1,528,519 did not. Of the Factor V carriers, 19 experienced an acute myocardial infarction, while 5,542 individuals from the general population experienced an acute myocardial infarction. The preliminary univariate analysis illustrated a mildly higher rate of myocardial infarctions in patients carrying the FVL mutation, 0.6% of patients (19/3,153) with FVL vs. 0.4% of patients (5,542/1,528,519) who lacked the mutation, *p*-value 0.025 (**Table 1**). A multivariate analysis of the FVL carriers was then conducted, adjusting for diabetes, hypertension, hyperlipidemia, race, and gender. The odds ratio (OR) for AMI in individuals positive for FVL was 1.63 with 95% CI 1.03-2.57 and a *p*-value 0.04, indicating a preliminary statistically significant finding (**Table 2**). This multivariate analysis was then adjusted for age, and the OR for AMI decreased to 1.44 with 95% CI 0.913-2.273 and a *p*-value 0.117, ultimately indicating a non-statistically significant finding when adjusted for age (**Table 3**).

Table 3. Multivariate analysis, with age adjustment, of patients under 40 with FVL in 2016

	P-value	OR	95% CI for OR	
			Lower	Upper
MI	0.117	1.440	0.913	2.273
Diabetes	0.301	1.099	0.919	1.313
Hypertension	0.000	1.341	1.191	1.510
Hyperlipidemia	0.421	1.191	0.778	1.822
Race (white)	0.000	4.169	3.808	4.564
Gender (female)	0.000	1.774	1.612	1.952
Age	0.000	0.952	0.946	0.958

Using the same univariate and multivariate analysis parameters, we examined the available population above 18, now totaling 4,552,932 individuals. In the expanded population, 8,205 individuals were carriers of FVL, while 4,544,727 individuals did not carry the mutation. Univariate analysis of this expanded population showed that 2.9% (242/8,205) of the FVL mutation carriers experienced an AMI, while 4.4% (199,349/4,544,727) of the patients without the FVL mutation experienced an AMI (**Table 4**). This was a notable change to the prior age-restricted demographic, which initially indicated that acute myocardial infarction occurred at a higher rate in the FVL carrier population. The final multivariate analysis of individuals with FVL over 18 showed no correlation between FVL and acute myocardial infarction with an OR of 0.757, a 95% CI 0.716-0.800, and a *p*-value of 0.0 (**Table 5**).

Table 4. Univariate analysis of all patients over 18 with and without Factor V Leiden and myocardial infarction in 2016

	FVL positive		FVL negative	
	FVL & AMI	FVL & No AMI	No FVL & AMI	No FVL & No AMI
Total	242	7963	199107	4345620
Percent	2.9%	97.1%	4.4%	95.6%

4.4% of the total population experienced an AMI. Total population = 4,552,932. FVL: Factor V Leiden. AMI: Acute Myocardial Infarction.

Table 5. Multivariate analysis, with age adjustment, of all patients over 18 with FVL in 2016

	P-value	OR	95% CI for OR	
			Lower	Upper
MI	0.000	0.757	0.716	0.800
Diabetes	0.009	0.970	0.948	0.992
Hypertension	0.000	1.044	1.023	1.065
Hyperlipidemia	0.000	1.363	1.299	1.430
Race (white)	0.000	3.819	3.727	3.913
Gender (female)	0.000	1.260	1.238	1.282
Age	0.000	1.013	1.013	1.014

Discussion

The correlation between Factor V Leiden mutation and the increased risk of venous thrombus formation has been well-established in scientific literature [1, 26]. However, an association between Factor V Leiden and acute myocardial infarction (AMI) has not been definitively proven, nor has a consensus regarding an increased risk profile been obtained. This discrepancy is likely due to variable study designs, the prevalence of FVL mutation in the observed population, and the rate at which people are screened for and diagnosed with FVL in the general public. However, one could theorize that the most common genetically inheritable hypercoagulable disease in Caucasians, FVL, would be correlated with an increased incidence of acute myocardial infarctions, especially in a younger population where individuals have less time to acquire chronic predisposing conditions such as diabetic complications and coronary artery disease [27-29]. Our goal in conducting this research was to determine if a statistically significant association between FVL and AMI exists by utilizing an extensive national medical database as our search engine to perform the retrospective analysis.

Table 6. Demographics of the sampled population

	N
Age	30188612
Female	58.2%
Male	41.8%
White	64.9%
Black	14.5%
Hispanic	10.4%
Asian/Pacific Islander	2.6%
Native American	0.6%
Other	7.1%
	57.2

Mean age: 57.51. Standard deviation: 20.331.

Our preliminary analysis demonstrated that FVL was an increased risk factor for AMI, which correlated with a large meta-analysis published in the Lancet in 2006 that concluded: "specific variants in Factor V might be associated with moderate increases in the risk of coronary disease... [21]". A significant limitation of this study was its inability to stratify for age as it was a meta-analysis. Notably, age stratification was the variable in our study that modified our results from being statistically significant in favor of FVL increasing the risk of AMI to becoming insignificant across both age groups. An Italian case-control study published in 2010 likewise recognized the importance of age stratification in determining AMI risk in FVL patients. However, unlike our study, they concluded that FVL was associated with an increased risk of AMI, the association remaining significant after adjustment for traditional coronary risk factors, including hypertension, smoking, diabetes, hypercholesterolemia, and BMI [28]. Their data, although significant, was only obtained from one region, most notably a region geographically rich with European Caucasians in whom FVL is typically identified. The demographic distribution of our study was much more diverse. Women comprised 58.2% of the population, while 41.8% were men. An ethnic breakdown is as follows: 64.9% White, 14.5% Black, 10.4% Hispanic, 2.6% Asian/Pacific Islander, 0.6% Native American, and 7.1% Other (**Table 6**).

Our retrospective observational analysis found no association between Factor V Leiden and acute myocardial infarctions when the data was adjusted for age. The dichotomy of results

across the literature demonstrates that further investigation into this topic is warranted, preferably with more extensive multinational studies to provide a much more diverse and comprehensive population pool. Herein lies the strength of our data collection method. The NIS aggregates its data from nationwide centers in one large pool, which can be stratified by age and other medical comorbidities. A significant limitation of our study centers around the accurate use of ICD-10 billing codes and the patients who experienced an AMI having the diagnosis of FVL when presenting to the hospital.

Conclusion

In our large retrospective observational analysis of patients with FVL, using univariate and multivariate analysis, we found no association between FVL and acute myocardial infarction when stratified for age across both examined populations.

Limitation

Our study's primary limitation centers around the ICD-10 coding of patients with FVL admitted for AMI. For a patient to be counted in our analysis, they likely would have required a pre-existing diagnosis of Factor V Leiden upon entering the hospital, as this is not a condition routinely screened for in patients with acute heart attacks. Future investigations would benefit from collecting a base of known FVL-positive patients and following them longitudinally to track the development of AMI. This type of study would be technically difficult but could provide a different perspective on the data. This research would be beneficial to primary care as well as in-patient hospital teams if it is determined that FVL-positive individuals are at greater risk for acute myocardial infarctions.

Disclosure of conflict of interest

None.

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