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Comorbidities associated with different levels of total cholesterol in male and female acute ischemic stroke patients

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Abstract

Men and women differ in their clinical risk factors with respect to various predictors of severity in acute ischemic stroke (AIS). High cholesterol is a risk factor for AIS and the mechanism by which high cholesterol levels lead to an AIS is well established. However, the specific relationship between demographic, clinical risk factors, total cholesterol, and the resulting gender difference in AIS patients is yet to be investigated. This study recruited AIS patients between January 2000 and June 2016 classified into normal, borderline or high total cholesterol (TC). Normal was defined as ≤200 mg/dl, borderline 200 to 239 mg/dl and high ≥240 mg/dl based on Adult Treatment Panel III (ATP III) Guidelines for the classification of TC levels. The logistic regression model was used to predict clinical risk factors associated within men and women AIS patients with different levels of TC. A total of 3532 AIS patients presented with normal TC, 760 patients with borderline TC and 427 patients with high TC. The high total cholesterol group was more likely to be women with increasing age (OR = 1.028, 95% CI, 1.006–1.052, $P = .014$), body mass index (BMI) (OR = 1.052, 95% CI, 1.004–1.102, $P = .033$), and high-density lipoprotein cholesterol (HDL-C) (OR = 1.039, 95% CI, 1.019–1.060, $P < .001$), while those with coronary artery disease (OR = 0.435, 95% CI, 0.234–0.809, $P = .003$), history of drug or alcohol abuse (OR = 0.261, 95% CI, 0.079–0.867, $P = .028$), increasing INR (OR = 0.187, 95% CI, 0.047–0.748, $P = .018$), and elevated diastolic blood pressure (OR = 0.982, 95% CI, 0.970–0.995, $P = .006$) were associated with being a male AIS patient. There were disparities in demographic and clinical risk factors associated with high TC levels in men when compared to women and more clinical risk factors were associated with high TC levels in men when compared to women with AIS. It is important to take into account specific clinical risk factors associated with gender-related differences in total cholesterol in AIS population to facilitate personalizing their therapeutic actions.

Abbreviations: Adjusted OR = adjusted odd ratio, Afib = atrial fibrillation, AIS = acute ischemic stroke, BMI = Body Mass Index, CAD = coronary artery disease, CHF = congestive heart failure, CI = confidence interval, CT = computer tomography, HDL-C = high-density lipoprotein cholesterol, HRT = hormone replacement therapy, INR = international normalized ratio, INR = international normalized ratio, IRB = Institutional Review Board, LDL- C = low-density lipoprotein cholesterol, MCA = middle cerebral artery, MRI = Magnetic Resonance Imaging, NIHSS = National Institute of Health Stroke Scale, PVD = peripheral vascular disease, ROC = receiver operating curve, rtPA = recombinant tissue plasminogen, TC = total cholesterol, TG = triglyceride, TIA = transient ischemic attack.

Keywords: cholesterol, gender, ischemic stroke, men stroke, women stroke

Editor: Ismaheel Lawal.

This study was funded by Fullerton Foundation Grant.

All authors have provided the corresponding author with permission to be named in the manuscript and consented to the submission of this manuscript.

The retrospective datasets are available by request from the corresponding author of this manuscript respectively.

The authors declare no conflicts of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Brechtel L, Poupore N, Stoikov T, Roley LT, Emerson JF, Nathaniel T. Comorbidities associated with different levels of total cholesterol in male and female acute ischemic stroke patients. Medicine 2020;99:52(e23870).

Received: 21 April 2020 / Received in final form: 31 October 2020 / Accepted: 23 November 2020

http://dx.doi.org/10.1097/MD.0000000000023870

1. Introduction

Stroke is a leading cause of death in both men and women, and the fourth leading cause of mortality among women between the ages of 20 and 59.[1] Moreover, women account for an estimated 60% of all stroke deaths,[2] and stroke represents the second leading cause of death in women older than 60 years. Among first-ever stroke patients, women are more likely to be older, have hypertension, atrial fibrillation (Afib), cardioembolic infarction and reduced mortality, and length of hospitalization.[3] More recovering women acute ischemic stroke (AIS) patients need assistance with activities of daily living and walking, and more frequently live in nursing homes after their stroke. Six months post stroke treatment, women are known to present with more severe disabilities when compared with recovering men AIS patients.[4] The Framingham Heart Study found that AIS women presented with more disability, and are 3.5 times more likely to be institutionalized at 3 to 6 months post-stroke compared with men.[5] Findings from this study also indicate that women present with a higher lifetime risk for stroke, likelihood of presenting with a recurrent stroke, and are more likely to have more severe strokes when compared with men.[2] In general, stroke among women is a major public health problem.

Men and women differ in their clinical risk factors with respect to various predictors of severity among AIS patients.[6] While the exact reason for this phenomenon is not clear, some studies have reported a correlation between stroke and changes in arterial structure and that biochemical variables including triglyceride level and total cholesterol levels may contribute to stroke severity.[7] While the role of triglycerides in the risk of ischemic stroke remains controversial,[8,9] a strong association between elevated levels of triglycerides and increased risk of ischemic stroke in men and women in the general population has been reported.[10] Increased level of triglycerides is known to indicate the presence of increased levels of remnants from very low-density lipoproteins.[11,12] These cholesterol-containing, triglyceride-rich lipoproteins could infiltrate the arterial endothelium,[13] get trapped within the subendothelial space[14] resulting in the development of atherosclerosis plaque that may cause ischemic stroke.[15] In general, elevated triglyceride levels were associated with increased risk of Ischemic stroke in men and women.[16,17]

Total cholesterol (TC) is a significant independent predictor of stroke severity and poor outcomes in patients with AIS.[18] A significant association between gender and serum levels of TC, LDL-C, and HDL-C in stroke patients has been reported.[19] Findings reveal that serum levels of all 3 factors and in particular TC, were higher in women than men with AIS patients,[20] indicating a gender-dependent relationship between the level of serum TC and the severity of AIS. A possible interaction between TC and different clinical risk factors including hypertension (HTN), diabetes mellitus (DM), among others has been proposed to contribute to the observed gender-related difference in stroke severity.[21] However, the relationship between specific demographic, clinical risk factors, total cholesterol, and the resulting gender difference in AIS patients is yet to be investigated.

The objective of this study is to identify clinical risk factors associated with different levels of total cholesterol and determine whether these factors were different between men and women who present with an AIS. Understanding the gender specific clinical risk factors that are associated with different levels of total cholesterol among male and female AIS will provide information about the measurable and qualitative risks of total cholesterol that can be managed to improve eligibility for thrombolytic therapy in AIS patients.

2. Methods

2.1. Study population

This is a retrospective and IRB approved study on patients with AIS who were admitted to the PRISMA Health Upstate in Greenville SC, USA between January 2010 and June 2016. This study was approved by the institutional review board of PRISMA Health institutional committee for ethics (approval number: 00052571). Patients that presented with an AIS based on pathologic lesions on brain MRI or CT were included for analysis. We used data for patients presenting to the hospital within 24 hours after the onset of AIS. This is because early admission is known to reduce poor outcome compared with 48 hours.[22,23] Data on patients with a suspicion of subarachnoid hemorrhage through CT findings (ICH, SAH, or other major infarct signs) was considered as a contraindication, and patients in this category were excluded. Demographics, clinical characteristics, laboratory values, and other pertinent data were obtained from a stroke registry; this registry has been described in previous studies.[24–29] Data on total cholesterol levels classified as normal ($\leq$200 mg/dl), borderline (200–239 mg/dl), and high ($\geq$240 mg/dl) based on the ATP III Guidelines[30] were collected. Data collected for medical history include atrial fibrillation, coronary artery disease (CAD), carotid stenosis, depression, diabetes, history of drug or alcohol abuse, dyslipidemia, family history of stroke, heart failure (HF), hormone replacement therapy (HRT), hypertension, migraine, obesity, prior stroke, prior TIA, prosthetic heart valve, peripheral vascular disease (PVD), chronic renal disease, sickle cell, sleep apnea, and history of smoking. All variables had the appropriate data reported. Information on patients' ambulatory data were also collected. Ambulatory data were coded on a 0 to 3 scale: undocumented (0), patients not able to ambulate (1), able to ambulate with assistance (2), and able to ambulate independently (3). The differences in a patient's score between admission and discharge was calculated to define if an improvement in ambulation was made. The validity of the scoring has been determined in a previous study.[31] In addition, patient demographic variables were analyzed. These included ages, race, gender, ethnicity, Body Mass Index (BMI), medication history, and stroke severity determined by the National Institutes of Health Stroke Scale (NIHSS) score. Lastly, the location where patients first received care (emergency department or direct admission to neurology unit) were collected and analyzed.

2.2. Statistical analysis

All statistics were performed using the Statistical Package for Social Sciences v 25.0 for Windows (SPSS, Chicago, IL). A one-way ANOVA was used to determine differences between the 3 levels of total cholesterol including normal ($\leq$200 mg/dl), borderline (200–239 mg/dl) and high ($\geq$240 mg/dl). The population was divided based on their cholesterol level on presentation. These 3 groups were then individually divided based on gender (men and women). In the cholesterol cohort, men and women group comparisons of demographic and clinical characteristics were analyzed using Student t test was for continuous variables while Man–Whitney U or Pearson Chi-Squared test as appropriate was used to analyze discrete variables to determine comparisons between the 2 men and women AIS patients. Since our study has a non-randomized design, a post hoc adjusted analysis (logistic regression) was used to determine demographic and clinical risk factors associated with different levels of total cholesterol as major outcomes based on gender.

For the regression model, the different levels for total cholesterol (normal, borderline, and high) were used as the dependent variable, while demographic and clinical risk factors for the men or women AIS patients were included in the model as primary independent variables. The specific clinical or demographic associated with normal, borderline and high levels of cholesterol levels were analyzed separately to determine differences in men and women AIS patients for each classification of the total cholesterol. The resulting odds ratios (ORs) were used to determine demographic or clinical risk factors associated with different levels of total cholesterol. Odd ratios of 95% confidence intervals (95% CIs) were considered and significance level was set at the probability level of $P < .05$. Multicollinearity and interactions were checked among independent variables using Hosmer-Lemeshow test. The overall correct classification percentage and the area under the receiver operating curve (AUROC) for score prediction was determined to test the sensitivity, specificity, and accuracy of the model.

3. Results

A total of 4719 AIS patients were identified. Of this, 3532 patients presented with normal total cholesterol (<200 mg/dl), 760 patients with a borderline high total cholesterol (200–239 mg/dl), while 427 patients presented with a high total cholesterol (≥240 mg/dl). Table 1 presents the demographic and clinical variables of AIS patients divided by their cholesterol levels. The normal total cholesterol group was older (67.96 ± 14.71 vs 63.75 ± 14.24 vs 64.26 ± 13.48) and more likely to be Caucasian (79.2% vs 76.7% vs 72.8), present with higher rates of Afib (18.9% vs 8.8% vs 9.6), coronary artery disease (32.4% vs 21.8% vs 23.9), dyslipidemia (53.1% vs 39.9% vs. 48.7), heart failure (11.5% vs 5.3% vs 8.0%), history of previous stroke (26.9% vs 23.3% vs 22.0%), chronic renal disease (8.3% vs 5.3% vs 7.5%), serum creatinine levels (1.26 ± 1.09 vs 1.15 ± 0.97 vs 1.21 ± 0.8) and INR (1.14 ± 0.43 vs 1.06 ± 0.37 vs 1.07 ± 0.49). The normal total cholesterol group presented with higher rates of taking an anti-HTN medication (72.3% vs. 60.9% vs 62.3%) and cholesterol reducer (50.2% vs 25.8% vs 28.8%).

The high total cholesterol group was more likely to be women (62.3% vs 56.2% vs 48.1%) and had a higher BMI (29.43 ± 6.75 vs 29.24 ± 7.12 vs 28.23 ± 7.02), present with diabetes (40.0% vs 32.1% vs 35.1%), family history or stoke (11.2% vs 11.2% vs 8.7%), obesity (52.2% vs 48.3% vs 41.1), higher levels of total cholesterol (276 ± 61.98 vs 216.94 ± 10.93 vs 149.55 ± 29.18), triglycerides (227.33 ± 183.09 vs 177.57 ± 119.7 vs 120.9 ± 77.91), high-density lipoprotein cholesterol (HDL-C; 46.83 ± 15.7 vs 45.76 ± 15.99 vs 40.32 ± 12.76), low-density lipoprotein cholesterol (LDL-C;185.63 ± 35.12 vs 185.63 ± 35.12 vs 87.52 ± 25.85), higher lipids (7.34 ± 2.56 vs 6.69 ± 2.16 vs 6.38 ± 2.63), and blood glucose (173 ± 104.71 vs 151.4 ± 88.28 vs 141.69 ± 72.3).

Table 2 presents clinical and demographic characteristics of the men and women AIS patients stratified by their total cholesterol levels. In the normal total cholesterol group, women were older (69.84 ± 15.96 vs 66.22 ± 13.22) and presented with higher BMI (28.55 ± 7.97 vs 27.93 ± 5.99), atrial fibrillation (29.1% vs 16.2%), depression (15.9% vs 10.4%), family history of stroke (9.8% vs. 7.6%), heart failure (13.4% vs. 9.7%), migraine (4.5% vs 0.9%), and with lower rates of coronary artery disease (27.1% vs 37.3%), carotid artery stenosis (5.1% vs 6.9%), history or drug or alcohol abuse (2.7% vs 8.8%), dyslipidemia (51.0% vs 55.0%), sleep apnea (2.1% vs 4.1%) and history of smoking (20.6% vs 31.9%). They presented with higher cholesterol (152.13 ± 28.61 vs 147.15 ± 29.5), high-density lipoprotein cholesterol (HDL-C) 43.23 ± 13.04 vs 37.61 ± 11.87), but with lower triglyceride levels (118.16 ± 77.54 vs 123.44 ± 78.19) and serum creatinine (1.15 ± 1.1 vs 1.36 ± 1.07). Men were less likely to be taking anti-HTN medications (70.0% vs 74.8%), antidepressants (9.4% vs 16.5%) and presented with lower NIHSS scores (7.53 ± 7.72 vs 8.87 ± 8.35), lower heart rates (82.28 79.02 ± 17.26 vs ± 17.78) and diastolic blood pressures (79.31 ± 18.87 vs. 83.31 ± 17.6).

Among patients with borderline cholesterol, women were older (66.72 ± 15.01 vs 59.93 ± 12.19) and presented with higher rates of depression (19.4% vs 9.9%), dyslipidemia (44.0% vs 34.5%), heart failure (7.3% vs 2.7%), hypertension (79.4% vs 70.9%), but with lower rates for histories of drug or alcohol abuse (3.0% vs 10.5%) and smoking (24.8% vs 46.8%). Men in the borderline group took less anti-HTN medications (50.5% vs 69.1%), cholesterol reducers (21.0%) vs 29.5%) and antidepressants (9.6% vs 19.2).

In the high total cholesterol group, women were older (66.6 ± 13.86 vs 60.23 ± 11.77) and presented with higher rates of atrial fibrillation (11.9% vs 5.7%), depression (15.9% vs 8.9%), and history of previous TIA (>24 hours) (10.4% vs 4.5%). Men in this group presented with higher rates of coronary artery disease (29.9% vs 20.4%) a history of drug or alcohol abuse (14.6% vs 3.3%) sleep apnea (5.7% vs 1.9%) and history of smoking (36.3% vs 24.1%).

Figure 1 presents the results for the multivariate analysis adjusting for the confounding effects of non-significant variables in AIS patients with normal total cholesterol. As shown in the figure, increasing age (OR = 1.009, 95% CI, 1.002–1.017, $P = .013$), higher BMI (OR = 1.03, 95% CI, 1.015–1.044, $P < .001$), depression (OR = 1.632, 95% CI, 1.083–2.461, $P = .019$), heart failure (OR = 1.687, 95% CI, 1.27–2.242, $P < .001$), migraine (OR = 4.119, 95% CI, 2.236–7.587, $P < .001$), anti-HTN medication (OR = 1.308, 95% CI, 1.05–1.63, $P = .017$), antidepressant medication (OR = 1.671, 95% CI, 1.11–2.515, $P = .014$),increasing NIHSS score (OR = 1.021, 95% CI, 1.008–1.033, $P < .001$), higher HDL-C (OR = 1.044, 95% CI, 1.036–1.052, $P < .001$), and higher heart rate (OR = 1.016, 95% CI, 1.011–1.022, $P < .001$) were associated with women. Coronary artery disease (OR = 0.565, 95% CI, 0.462–0.691, $P < .001$), history of drug or alcohol abuse (OR = 0.265, 95% CI, 0.167–0.421, $P < .001$), dyslipidemia (OR = 0.782, 95% CI, 0.648–0.944, $P = .01$), sleep apnea (OR = 0.303, 95% CI, 0.182–0.505, $P < .001$), higher serum creatinine (OR = 0.784, 95% CI, 0.694–0.884, $P < .001$), increasing diastolic blood pressure (OR = 0.977, 95% CI, 0.972–0.982, $P < .001$), and receiving rtPA (OR = 0.792, 95% CI, 0.653–0.96, $P = .017$) were associated with men in the normal total cholesterol group. The ROC curve for the predictive power of the regression model is presented in Figure 2. The discriminating capability of the model was strong as shown by the ROC curve, with area under the curve (AUROC) of AUROC = 0.746 (95% CI, 0.730–0.763, $P < .001$).

In the group with a borderline cholesterol (Fig. 3), anti-HTN medication (OR = 1.601, 95% CI, 1.093–2.345, $P = .016$), antidepressant medication (OR = 2.239, 95% CI, 1.328–3.776, $P = .002$),higher HDL-C (OR = 1.033, 95% CI, 1.018–1.048, $P < .001$), and increasing heart rate (OR = 1.028, 95% CI, 1.016–1.04, $P < .001$) were more likely to be associated with women. History of drug or alcohol abuse (OR = 0.39, 95% CI, 0.179–0.847, $P = .017$), history of smoking (OR = 0.597, 95% CI, 0.409–0.871, $P = .008$), increasing diastolic blood pressure (OR = 0.971, 95% CI, 0.961–0.981, $P < .001$), and improvement in ambulation (OR = 0.570, 95% CI, 0.391–0.831, $P = .003$) were associated with men AIS patients in this group. The ROC curve for the predictive power of the regression model is presented in Figure 4. The discriminating capability of the model was strong as shown by the ROC curve, with area under the curve (AUROC) of AUROC = 0.780 (95% CI, 0.745–0.814, $P < .001$).

In the group with a high total cholesterol (Fig. 5), increasing age (OR = 1.028, 95% CI, 1.006–1.052, $P = .014$), higher BMI (OR = 1.052, 95% CI, 1.004–1.102, $P = .033$), and increasing HDL-C (OR = 1.039, 95% CI, 1.019–1.060, $P < .001$), were more likely to be associated with the women AIS patients. Coronary artery disease (OR = 0.435, 95% CI, 0.234–0.809, $P = .003$), history of drug or alcohol abuse (OR = 0.261, 95% CI, 0.079–0.867, $P = .028$), increasing INR (OR = 0.187, 95% CI, 0.047–0.748, $P = .018$), and elevated diastolic blood pressure (OR = 0.982, 95% CI, 0.970–0.995, $P = .006$) were associated with men AIS patients. The ROC curve for the predictive power

Table 1

Demographic and clinical characteristics of AIS patients. Results for continuous variables are presented as Mean ± SD, while discrete data are presented as percentage frequency. Pearson's Chi-Squared and One-way ANOVA were used to compare differences between demographic and clinical characteristics in normal, borderline high, and high levels of total cholesterol.

Characteristic	Normal Total Cholesterol (<200 mg/dl)	Borderline High Total Cholesterol (200–239 mg/dl)	High Total Cholesterol (≥240 mg/dl)	*P* value
Number of patients	3532	760	427	
Age Group: No. (%)				
<50	402 (11.4)	117 (15.4)	57 (13.3)	<.001*,a
50–59	602 (17.0)	182 (23.9)	109 (25.5)	
60–69	818 (23.2)	194 (25.5)	114 (26.7)	
70–79	828 (23.4)	153 (20.1)	81 (19.0)	
>=80	882 (25.0)	114 (15.0)	66 (15.5)	
Mean ± SD	67.96 ± 14.71	63.75 ± 14.24	64.26 ± 13.48	<.001*,b
Race: No (%)				
White	2798 (79.2)	583 (76.7)	311 (72.8)	.031*,a
Black	621 (17.6)	149 (19.6)	100 (23.4)	
Other	113 (3.2)	28 (3.7)	16 (3.7)	
Gender: No. (%)				
Female	1700 (48.1)	427 (56.2)	270 (63.2)	<.001*,a
Male	1832 (51.9)	333 (43.8)	157 (36.8)	
Hispanics	59 (1.7)	7 (0.9)	11 (2.6)	.091
BMI: Mean ± SD	28.23 ± 7.02	29.24 ± 7.12	29.43 ± 6.75	<.001*,b
Medical History: No. (%)				
Atrial fibrillation	669 (18.9)	67 (8.8)	41 (9.6)	<.001*,a
Coronary Artery Disease	1144 (32.4)	166 (21.8)	102 (23.9)	<.001*,a
Carotid Artery Stenosis	214 (6.1)	41 (5.4)	24 (5.6)	.753
Depression	461 (13.1)	116 (15.3)	57 (13.3)	.268
Diabetes	1240 (35.1)	244 (32.1)	171 (40.0)	.023*,a
Drugs or Alcohol	207 (5.9)	48 (6.3)	32 (7.5)	.393
Dyslipidemia	1874 (53.1)	303 (39.9)	208 (48.7)	<.001*,a
Stroke Family History	306 (8.7)	85 (11.2)	48 (11.2)	.033*,a
Heart Failure	405 (11.5)	40 (5.3)	34 (8.0)	<.001*,a
Hormonal Replacement Therapy	62 (1.8)	12 (1.6)	2 (0.5)	.136
Hypertension	2797 (79.2)	575 (75.7)	339 (79.4)	.091
Migraine	93 (2.6)	20 (2.6)	13 (3.0)	.881
Obesity	1453 (41.1)	367 (48.3)	223 (52.2)	<.001*,a
Previous Stroke	951 (26.9)	177 (23.3)	94 (22.0)	.018*,a
Previous TIA (> 24 hours)	333 (9.4)	66 (8.7)	35 (8.2)	.614
Prosthetic Heart Valve	45 (1.3)	5 (0.7)	5 (1.2)	.357
Peripheral Vascular Disease	253 (7.2)	42 (5.5)	31 (7.3)	.260
Chronic Renal Disease	294 (8.3)	40 (5.3)	32 (7.5)	.016*,a
Sickle Cell	2 (0.1)	0 (0.0)	1 (0.2)	.291
Sleep Apnea	111 (3.1)	28 (3.7)	14 (3.3)	.746
Smoker	934 (26.4)	262 (34.5)	122 (28.6)	<.001*,a
Medication History: No (%)				
Anti-HTN medication	2554 (72.3)	463 (60.9)	266 (62.3)	<.001*,a
Cholesterol Reducer	1774 (50.2)	196 (25.8)	123 (28.8)	<.001*,a
Diabetes medication	993 (28.1)	181 (23.8)	118 (27.6)	.054
Antidepressant	452 (12.8)	114 (15.0)	54 (12.6)	.252
Initial NIHSS Score: No (%)				
0–9	2260 (71.7)	547 (78.3)	290 (74.2)	.024*,a
10–14	358 (11.4)	63 (9.0)	35 (9.0)	
15–20	352 (11.2)	55 (7.9)	42 (10.7)	
21–25	181 (5.7)	34 (4.9)	24 (6.1)	
Mean ± SD	8.17 ± 8.06	7 ± 7.46	7.28 ± 7.41	<.001*,b
Lab values: Mean ± SD				
Total cholesterol	149.55 ± 29.18	216.94 ± 10.93	276 ± 61.98	<.001*,b
Triglycerides	120.9 ± 77.91	177.57 ± 119.7	227.33 ± 183.09	<.001*,b
HDL	40.32 ± 12.76	45.76 ± 15.99	46.83 ± 15.7	<.001*,b
LDL	87.52 ± 25.85	140.72 ± 23.46	185.63 ± 35.12	<.001*,b
Lipids	6.38 ± 2.63	6.69 ± 2.16	7.34 ± 2.56	<.001*,b
Blood Glucose	141.69 ± 72.3	151.4 ± 88.28	173 ± 104.71	<.001*,b
Serum Creatinine	1.26 ± 1.09	1.15 ± 0.97	1.21 ± 0.8	.049*,b
Initial Platelet Count	119918.81 ± 131015.85	144972.89 ± 130960.98	155667.04 ± 139616.67	.058

(*continued*)

Table 1
(continued).

Characteristic	Normal Total Cholesterol (<200 mg/dl)	Borderline High Total Cholesterol (200–239 mg/dl)	High Total Cholesterol (≥240 mg/dl)	*P* value
INR	1.14 ± 0.43	1.06 ± 0.37	1.07 ± 0.49	<.001*,b
Vital Signs: Mean ± SD				
Heart Rate	80.59 ± 17.59	81.98 ± 17.1	83.29 ± 18.73	.003*,b
Blood Pressure Systolic	150.98 ± 28.17	158.96 ± 28.66	162.85 ± 30.19	<.001*,b
Blood Pressure Diastolic	81.38 ± 18.33	86.86 ± 18.38	88.24 ± 21.04	<.001*,b
Ambulation Status Prior to Event: No. (%)				
Ambulate Independently	3196 (90.5)	700 (92.1)	405 (94.8)	.059
Ambulate with Assistance	121 (3.4)	28 (3.7)	8 (1.9)	
Unable to Ambulate	125 (3.5)	19 (2.5)	12 (2.8)	
Not Documented	89 (2.5)	13 (1.7)	2 (0.5)	
Ambulation Status on Admission: No. (%)				
Ambulate Independently	843 (23.9)	217 (28.6)	107 (25.1)	<.001*,a
Ambulate with Assistance	1065 (30.2)	257 (33.8)	154 (36.1)	
Unable to Ambulate	1090 (30.9)	176 (23.2)	110 (25.8)	
Not Documented	534 (15.1)	110 (14.5)	56 (13.1)	
Ambulation Status on Discharge: No. (%)				
Ambulate Independently	1488 (42.1)	349 (45.9)	189 (44.3)	.092
Ambulate with Assistance	1196 (33.9)	265 (34.9)	141 (33.0)	
Unable to Ambulate	631 (17.9)	115 (15.1)	77 (18.0)	
Not Documented	217 (6.1)	31 (4.1)	20 (4.7)	
First Care Received: No. (%)				
Emergency Department	2813 (80.3)	617 (81.7)	338 (79.7)	.621
Direct Admission	689 (19.7)	138 (18.3)	86 (20.3)	
rtPA Administration	970 (27.5)	205 (27.0)	93 (21.8)	.044*,a
Improved Ambulation: No. (%)	1280 (38.5)	256 (35.1)	132 (32.4)	.021*,a
NIHSS > 7: No. (%)	1281 (38.7)	234 (32.4)	127 (31.7)	<.001*,a
Diastolic BP ≥ 80 mmHg: No. (%)	1786 (50.6)	489 (64.3)	270 (63.2)	<.001*,a

[a] Pearson Chi-Squared test.
[b] One-way ANOVA.
* *P* value < .05.

of the regression model is presented in Figure 6. The discriminating capability of the model was strong as shown by the ROC curve, with area under the curve (AUROC) of AUROC = 0.785 (95% CI, 0.733–0.836, $P < .001$).

4. Discussion

Our study shows that first, in an AIS population, 3532 patients presented with normal total cholesterol (≤200 mg/dl), 760 patients had a borderline high total cholesterol (200–239 mg/dl), while 427 patients presented with a high total cholesterol (≥240 mg/dl). Second, women AIS patients with normal total cholesterol are more likely to be older, depressed, have a history of migraines, and have a higher NIHSS score at presentation. They also are more likely to have a higher BMI, HDL-C, heart rate, and are more likely to be taking both anti-HTN medication and antidepressant medication. The men counterparts are more likely to present with coronary artery disease, history of drug or alcohol abuse, sleep apnea, serum creatinine, diastolic blood pressure, and are more likely to receive rtPA. Third, in the group with borderline high total cholesterol, anti-HTN medication, antidepressant medication, higher HDL-C, and increasing heart rate were more likely to be associated with women, while a history of drug or alcohol abuse, smoking, elevated diastolic blood pressure, and improvement in ambulation were associated with men. Finally, in AIS patients with a high total cholesterol, increasing age, BMI, and HDL-C, were more likely to be associated with the woman gender while coronary artery disease, history of drug or alcohol abuse, elevated INR, and diastolic blood pressure were associated with men AIS patients. These results reveal gender differences in demographic and clinical risk factors in AIS patients stratified by cholesterol levels; normal total cholesterol (<200 mg/dl), borderline high total cholesterol (200–239 mg/dl), and high total cholesterol (≥240 mg/dl). More importantly, it reveals that the clinical risk factors associated with normal cholesterol levels and high cholesterol levels in AIS patients are different between men and women.

Several studies have shown that women are more likely to present with stroke at an older age.[3,32,33] It has also been shown that women are more likely to have a severe stroke when compared to men.[3,34] In addition, the prevalence of hypertension, atrial fibrillation, dyslipidemia, and obesity are greater in women.[35–38] Consistent with other studies with evidence of gender differences,[39,40] in the present study, we found that women AIS patients with normal total cholesterol are more likely to be older, depressed and present with a higher NIHSS. Additionally, women are more likely to have a higher BMI, HDL-C level and heart rate; they are also more likely to present with migraine and are more likely to be taking anti-HTN medication and antidepressant medication. Their men counterparts are more likely to be dyslipidemic with coronary artery disease, and present with a history of drug or alcohol abuse, sleep apnea, serum creatinine, and a higher diastolic blood pressure. Notably, men are more likely to receive rtPA than women.

Our data also corroborates with previous studies,[41–44] that indicates a gender difference in clinical risk factors for AIS

Table 2

Demographic and clinical characteristics of AIS patients with different levels of total cholesterol stratified by gender. Results for continuous variables are presented as Mean ± SD, while discrete data are presented as percentage frequency. Pearson Chi-Squared is used to compare gender differences between demographic and clinical characteristics in groups of different total cholesterol levels.

	Normal Total Cholesterol (<200 mg/dL)			Borderline High Total Cholesterol (200-239 mg/dL)			High Total Cholesterol (≥240 mg/dL)		
Characteristic	**Male**	**Female**	***P* value**	**Male**	**Female**	***P* value**	**Male**	**Female**	***P* value**
Number of patients	1832	1700		333	427		157	270	
Age Group: No. (%)									
<50 years	185 (10.1)	217 (12.8)	<.001*,a	59 (17.7)	58 (13.6)	<.001*,a	24 (15.3)	33 (12.2)	<.001*,a
50-59	391 (21.3)	211 (12.4)		103 (30.9)	79 (18.5)		53 (33.8)	56 (20.7)	
60-69	495 (27.0)	323 (19.0)		103 (30.9)	91 (21.3)		49 (31.2)	65 (24.1)	
70-79	439 (24.0)	389 (22.9)		44 (13.2)	109 (25.5)		23 (14.6)	58 (21.5)	
>=80	322 (17.6)	560 (32.9)		24 (7.2)	90 (21.1)		8 (5.1)	58 (21.5)	
Age Mean ± SD	66.22 ± 13.22	69.84 ± 15.96	<.001*,b	59.93 ± 12.19	66.72 ± 15.01	<.001*,b	60.23 ± 11.77	66.6 ± 13.86	<.001*,b
Race: No (%)									
White	1453 (79.3)	1345 (79.1)	.783	256 (76.9)	327 (76.6)	.883	110 (70.1)	201 (74.4)	.593
Black	324 (17.7)	297 (17.5)		66 (19.8)	83 (19.4)		40 (25.5)	60 (22.2)	
Other	55 (3.0)	58 (3.4)		11 (3.3)	17 (4.0)		7 (4.5)	9 (3.3)	
Hispanics	29 (1.6)	30 (1.8)	.674	2 (0.6)	5 (1.2)	.414	2 (1.3)	9 (3.3)	.195
BMI: Mean ± SD	27.93 ± 5.99	28.55 ± 7.97	.009*,b	29.31 ± 6.71	29.19 ± 7.43	.830	28.87 ± 4.78	29.76 ± 7.67	.143
Medical History: No. (%)									
Atrial fibrillation	297 (16.2)	372 (21.9)	<.001*,a	23 (6.9)	44 (10.3)	.101	9 (5.7)	32 (11.9)	.038*,a
Coronary Artery Disease	684 (37.3)	460 (27.1)	<.001*,a	72 (21.6)	94 (22.0)	.897	47 (29.9)	55 (20.4)	.025*,a
Carotid Artery Stenosis	127 (6.9)	87 (5.1)	.024*,a	23 (6.9)	18 (4.2)	.103	10 (6.4)	14 (5.2)	.608
Depression	190 (10.4)	271 (15.9)	<.001*,a	33 (9.9)	83 (19.4)	<.001*,a	14 (8.9)	43 (15.9)	.040*,a
Diabetes	660 (36.0)	580 (34.1)	.235	102 (30.6)	142 (33.3)	.442	62 (39.5)	109 (40.4)	.858
Drugs or Alcohol	161 (8.8)	46 (2.7)	<.001*,a	35 (10.5)	13 (3.0)	<.001*,a	23 (14.6)	9 (3.3)	<.001*,a
Dyslipidemia	1007 (55.0)	867 (51.0)	.018*,a	115 (34.5)	188 (44.0)	.008*,a	67 (42.7)	141 (52.2)	.057
Stroke Family History	139 (7.6)	167 (9.8)	.018*,a	45 (13.5)	40 (9.4)	.072	21 (13.4)	27 (10.0)	.287
Heart Failure	178 (9.7)	227 (13.4)	.001*,a	9 (2.7)	31 (7.3)	.005*,a	15 (9.6)	19 (7.0)	.354
Hypertension	1440 (78.6)	1357 (79.8)	.372	236 (70.9)	339 (79.4)	.007*,a	119 (75.8)	220 (81.5)	.161
Migraine	17 (0.9)	76 (4.5)	<.001*,a	5 (1.5)	15 (3.5)	.086	3 (1.9)	10 (3.7)	.298
Obesity	768 (41.9)	685 (40.3)	.326	170 (51.1)	197 (46.1)	.178	91 (58.0)	132 (48.9)	.070
Previous Stroke	482 (26.3)	469 (27.6)	.392	70 (21.0)	107 (25.1)	.191	34 (21.7)	60 (22.2)	.892
Previous TIA (>24 hours)	159 (8.7)	174 (10.2)	.114	23 (6.9)	43 (10.1)	.124	7 (4.5)	28 (10.4)	.032*,a
Prosthetic Heart Valve	26 (1.4)	19 (1.1)	.425	1 (0.3)	4 (0.9)	.282	3 (1.9)	2 (0.7)	.278
Peripheral Vascular Disease	130 (7.1)	123 (7.2)	.873	19 (5.7)	23 (5.4)	.848	10 (6.4)	21 (7.8)	.589
Chronic Renal Disease	157 (8.6)	137 (8.1)	.583	23 (6.9)	17 (4.0)	.073	11 (7.0)	21 (7.8)	.770
Sleep Apnea	75 (4.1)	36 (2.1)	.001*,a	10 (3.0)	18 (4.2)	.379	9 (5.7)	5 (1.9)	.030*,a
Smoker	584 (31.9)	350 (20.6)	<.001*,a	156 (46.8)	106 (24.8)	<.001*,a	57 (36.3)	65 (24.1)	.007*,a
Medication History: No (%)									
Anti-HTN medication	1282 (70.0)	1272 (74.8)	.001*,a	168 (50.5)	295 (69.1)	<.001*,a	96 (61.1)	170 (63.0)	.709
Cholesterol Reducer	948 (51.7)	826 (48.6)	.061	70 (21.0)	126 (29.5)	.008*,a	48 (30.6)	75 (27.8)	.539
Diabetes medication	526 (28.7)	467 (27.5)	.412	72 (21.6)	109 (25.5)	.210	40 (25.5)	78 (28.9)	.447
Antidepressant	172 (9.4)	280 (16.5)	<.001*,a	32 (9.6)	82 (19.2)	<.001*,a	15 (9.6)	39 (14.4)	.143
Initial NIHSS Score: No (%)									
0–9	1230 (74.4)	1030 (68.8)	.005*,a	252 (81.8)	295 (75.4)	.194	105 (71.9)	185 (75.5)	.332
10–14	167 (10.1)	191 (12.8)		25 (8.1)	38 (9.7)		18 (12.3)	17 (6.9)	
15–20	167 (10.1)	185 (12.3)		18 (5.8)	37 (9.5)		14 (9.6)	28 (11.4)	
21–25	89 (5.4)	92 (6.1)		13 (4.2)	21 (5.4)		9 (6.2)	15 (6.1)	
Mean ± SD	7.53 ± 7.72	8.87 ± 8.35	<.001*,b	6.15 ± 6.63	7.66 ± 7.99	.006*,b	6.99 ± 7.2	7.46 ± 7.54	.539
Lab values: Mean ± SD									
Total cholesterol	147.15 ± 29.5	152.13 ± 28.61	<.001*,b	216.51 ± 10.65	217.28 ± 11.15	.335	278.23 ± 87.43	274.7 ± 40.58	.571
Triglycerides	123.44 ± 78.19	118.16 ± 77.54	.044*,b	198.04 ± 137.4	161.61 ± 101.17	<.001*,b	248.41 ± 221.6	215.03 ± 155.44	.098
HDL	37.61 ± 11.87	43.23 ± 13.04	<.001*,b	41.35 ± 14.9	49.17 ± 15.98	<.001*,b	41.78 ± 13.78	49.78 ± 16.01	<.001*,b
LDL	87.75 ± 26.74	87.26 ± 24.87	.575	140.87 ± 22.32	140.61 ± 24.34	.882	186.77 ± 36.88	184.97 ± 34.13	.616
Lipids	6.36 ± 1.58	6.41 ± 3.42	.573	6.87 ± 2.3	6.54 ± 2.03	.041*,b	7.44 ± 2.62	7.29 ± 2.53	.572
Blood Glucose	140.23 ± 66.39	143.28 ± 78.2	.212	157.16 ± 89.48	146.93 ± 87.19	.116	182.28 ± 105.98	167.6 ± 103.79	.164
Serum Creatinine	1.36 ± 1.07	1.15 ± 1.1	<.001*,b	1.22 ± 0.68	1.11 ± 1.14	.110	1.32 ± 0.86	1.15 ± 0.76	.037*,b
Initial Platelet Count	120714.88 ± 129436.92	119037.82 ± 133024.8	.899	136846.15 ± 121645.58	150482.54 ± 137667.46	.614	166549.29 ± 135933.57	150528.19 ± 142930.11	.701
INR	1.15 ± 0.45	1.13 ± 0.4	.150	1.05 ± 0.21	1.07 ± 0.46	.484	1.14 ± 0.77	1.02 ± 0.15	.093
Vital Signs: Mean ± SD									
Heart Rate	79.02 ± 17.26	82.28 ± 17.78	<.001*,b	80.09 ± 16.36	83.45 ± 17.54	.007*,b	84.25 ± 20.83	82.74 ± 17.41	.444
Blood Pressure Systolic	151.8 ± 27.93	150.1 ± 28.4	.073	159.83 ± 28.74	158.29 ± 28.6	.462	161.78 ± 31.5	163.47 ± 29.44	.579
Blood Pressure Diastolic	83.31 ± 17.6	79.31 ± 18.87	<.001*,b	91.57 ± 16.63	83.19 ± 18.85	<.001*,b	92.97 ± 20.4	85.49 ± 20.95	<.001*,b
Ambulation Status Prior to Event: No. (%)									
Ambulate Independently	1708 (93.2)	1488 (87.5)	<.001*,a	318 (95.5)	382 (89.5)	.006*,a	155 (98.7)	250 (92.6)	.051
Ambulate with Assistance	48 (2.6)	73 (4.3)		5 (1.5)	23 (5.4)		1 (0.6)	7 (2.6)	
Unable to Ambulate	50 (2.7)	75 (4.4)		4 (1.2)	15 (3.5)		1 (0.6)	11 (4.1)	
Not Documented	26 (1.4)	63 (3.7)		6 (1.8)	7 (1.6)		0 (0.0)	2 (0.7)	
Ambulation Status on Admission: No. (%)									
Ambulate Independently	495 (27.0)	348 (20.5)	<.001*,a	102 (30.6)	115 (26.9)	.017*,a	46 (29.3)	61 (22.6)	.051
Ambulate with Assistance	562 (30.7)	503 (29.6)		118 (35.4)	139 (32.6)		48 (30.6)	106 (39.3)	
Unable to Ambulate	493 (26.9)	597 (35.1)		59 (17.7)	117 (27.4)		36 (22.9)	74 (27.4)	
Not Documented	282 (15.4)	252 (14.8)		54 (16.2)	56 (13.1)		27 (17.2)	29 (10.7)	
Ambulation Status on Discharge: No. (%)									
Ambulate Independently	851 (46.5)	637 (37.5)	<.001*,a	176 (52.9)	173 (40.5)	.001*,a	77 (49.0)	112 (41.5)	.009*,a
Ambulate with Assistance	601 (32.8)	595 (35.0)		110 (33.0)	155 (36.3)		44 (28.0)	97 (35.9)	

(*continued*)

Table 2

(continued).

Characteristic	Normal Total Cholesterol (<200 mg/dL)			Borderline High Total Cholesterol (200-239 mg/dL)			High Total Cholesterol (≥240 mg/dL)		
	Male	Female	*P* value	Male	Female	*P* value	Male	Female	*P* value
Unable to Ambulate	274 (15.0)	357 (21.0)		33 (9.9)	82 (19.2)		23 (14.6)	54 (20.0)	
Not Documented	106 (5.8)	111 (6.5)		14 (4.2)	17 (4.0)		13 (8.3)	7 (2.6)	
rtPA administration: No. (%)	523 (28.5)	447 (26.3)	.134	91 (27.3)	114 (26.7)	.846	33 (21.0)	60 (22.2)	.771
First Care Received: No. (%)									
Emergency Department	1456 (80.3)	1357 (80.4)	.925	275 (83.1)	342 (80.7)	.393	122 (79.2)	216 (80.0)	.848
Direct Admission	358 (19.7)	331 (19.6)		56 (16.9)	82 (19.3)		32 (20.8)	54 (20.0)	
Improved Ambulation: No. (%)	685 (39.5)	595 (37.3)	.193	128 (40.1)	128 (31.1)	.012*,a	44 (30.3)	88 (33.5)	.520
NIHSS > 7: No. (%)	590 (34.4)	691 (43.3)	<.001*,a	90 (28.8)	144 (35.2)	.066	47 (31.8)	80 (31.6)	.977
Diastolic Blood Pressure ≥ 80 mmHg: No. (%)	1017 (55.6)	769 (45.3)	<.001*,a	259 (77.8)	230 (53.9)	<.001*,a	122 (77.7)	148 (54.8)	<.001*,a

[a] Pearson Chi-Squared test.

[b] Student's *t* test.

* *P* value <.05.

patients with borderline cholesterol level. A major finding in the current study is that even after adjustment for the effect of confounding variables, the effects of anti-HTN medication, antidepressant medication, increasing heart rate and elevated HDL-C which were associated with normal cholesterol level were retained in borderline cholesterol levels in the women AIS patients, while the effect of BMI, age, depression and NIH scores disappeared in borderline TC levels. In addition, the effect of dyslipidemia, coronary artery disease, sleep apnea, serum creatinine, and receiving rtPA, which were all significant in the normal TC level in men AIS patients were attenuated in the adjusted analysis for the borderline AIS, while the effect of

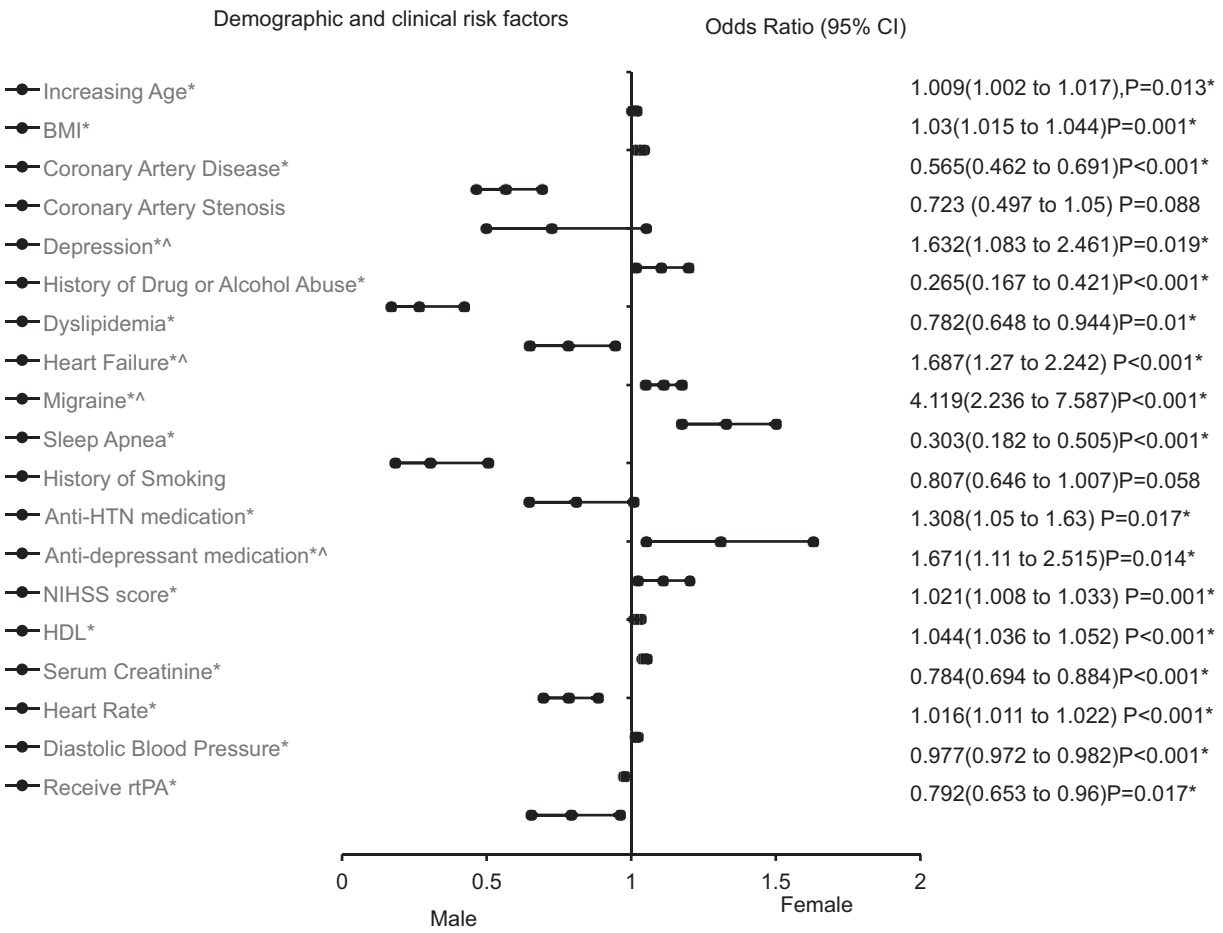

Figure 1. Forest plot representation of clinical factors that were associated with AIS population with normal total cholesterol (<200 mg/dl). Adjusted OR < 1 denote factors that are associated with being men while OR>1 denote factors that are associated with being women. Hosmer-Lemeshow test ($P = .257$), Cox & Snell ($R^2 = 0.179$). The overall classified percentage of 68.5% was applied to check for fitness of the logistic regression model. *Indicates statistical significance ($P < .05$) with a 95% confidence interval.

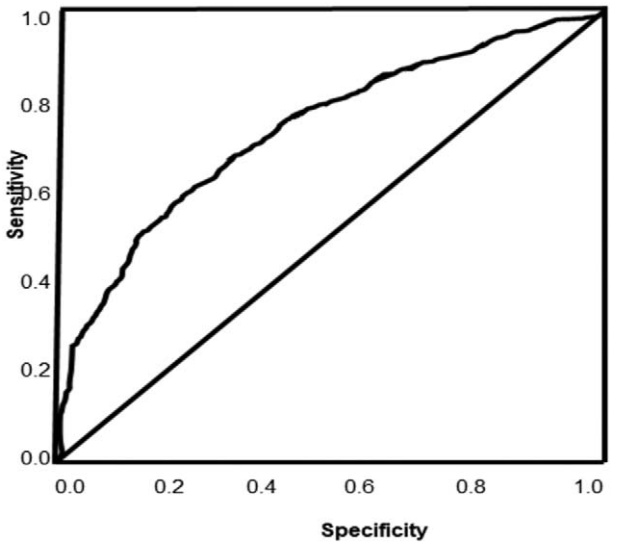

Figure 2. ROC curve for the predictive power of the regression model for AIS population with normal total cholesterol (<200 mg/dl). Higher area under the curve (AUC) values in ROC analysis indicate better discrimination of the score for the measured outcome. Classification table (overall correctly classified percentage = 68.5%) and area under the ROC curve (AUC = 0.746, 0.730–0.763) were applied to check model fitness.

diastolic blood pressure was retained. Moreover, the effects of drug or alcohol abuse, smoking, elevated diastolic blood pressure, and improvement in ambulation were revealed for men with borderline AIS TC.

Coronary artery disease, history of drug or alcohol abuse, and diastolic blood pressure were associated with normal TC levels for men AIS patients and were retained in the borderline and high TC levels, while INR, which was not associated with normal or borderline TC levels, appeared and was significant for men AIS with high TC. While coronary artery disease is well known to be associated with increased risk for stoke,[45–47] the association of a history of drug or alcohol abuse, increased diastolic blood pressure and related gender differences in AIS is not as clear. There is a documented link of cocaine use and stroke, with cocaine users demonstrating quicker clot formation with a decreased overall clot strength and therefore an increased association with ICH,[48] but other drugs and alcohol are not as well elucidated. Alcoholic withdrawal has been associated with poorer outcome in AIS patients,[49] but differences in gender and the impact of heavy alcohol use pre and post-stroke is not well studied. Although much is reported on the effects of hypertension on stroke, systolic versus diastolic effects have not been well investigated. Our findings indicate that though there are differences in demographic and clinical risk factors in men and women AIS with TC, similarities in clinical risk factors also

Figure 3

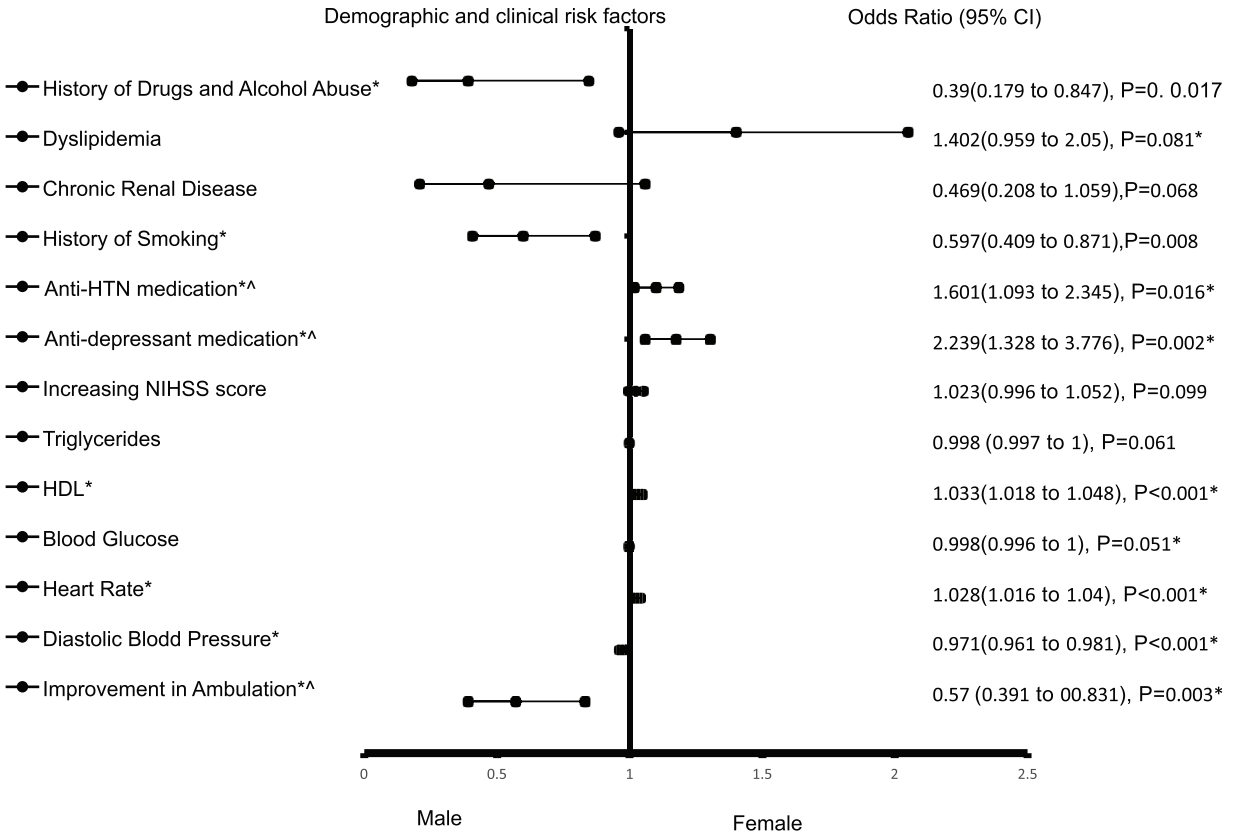

Figure 3. Forest Plot representation of clinical factors that were associated with AIS population with borderline total cholesterol (200–239 mg/dl). Adjusted OR < 1 denote factors that are associated with being men while OR > 1 denote factors that are associated with being women. Hosmer-Lemeshow test ($P = .581$), Cox & Snell ($R^2 = 0.224$). The overall classified percentage of 71.5% was applied to check for fitness of the logistic regression model. *Indicates statistical significance ($P < .05$) with a 95% confidence interval.

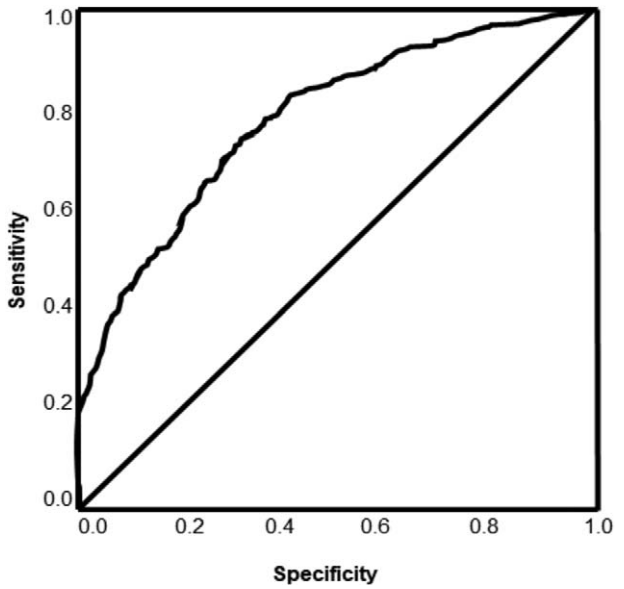

Figure 4. ROC curve for the predictive power of the regression model for AIS population with borderline total cholesterol (200–239 mg/dl). Higher area under the curve (AUC) values in ROC analysis indicate better discrimination of the score for the measured outcome. Classification table (overall correctly classified percentage = 71.5%) and area under the ROC curve (AUC = 0.780, 0.745–0.814) were applied to check model fitness.

persist in the normal and borderline levels of TC in both men and women AIS patients. While high cholesterol level is a major risk factor for coronary heart disease, its role in stroke and gender differences is not very clear. The mechanisms explaining the association between different TC levels and AIS is unknown.[50,51] However, the gender differences observed in this study could possibly be explained by differences in demographic and clinical risk factors, indicating that even when the issue of cholesterol maybe addressed in normal TC stroke patients, severity could still be enhanced by other clinical and demographic factors differently in both men and women AIS patients.

In the group with high total cholesterol levels, increasing age, BMI, and HDL-C was retained from the group with normal TC. However, only elevated HDL-C was present for all 3 groups; increasing age and BMI were not significant risk factors in the borderline TC group. Our finding that total high HDL-C is significantly elevated in the women compared to the men group may not be related to sex hormones because most of our women AIS patients were above the age of menopause or andropause. Menopause is associated with an increase in multiple stroke risk factors including triglycerides, total cholesterol and LDL-C but a decrease in HDL-C.[52] The average age of menopause is reported to be 51 years, with a range from 40 to 60 years.[50,53] The surgical induction of menopause without hormone replacement therapy revealed no effect on lipoprotein profile compared to hysterectomy with conservation of the ovaries.[54] Therefore, differences in men and women AIS patients in metabolism of lipoproteins might be associated with the synergy between the complex network of hormone actions with men or women-specific modulators of HDL-C metabolism, resulting in different expression of HDL-C between men and women. Moreover, several lines of evidence indicate that dyslipidemia is a major risk factor for stroke and that the alteration of LDL-C, a primary serum lipid biomarker, is an effective treatment in the secondary

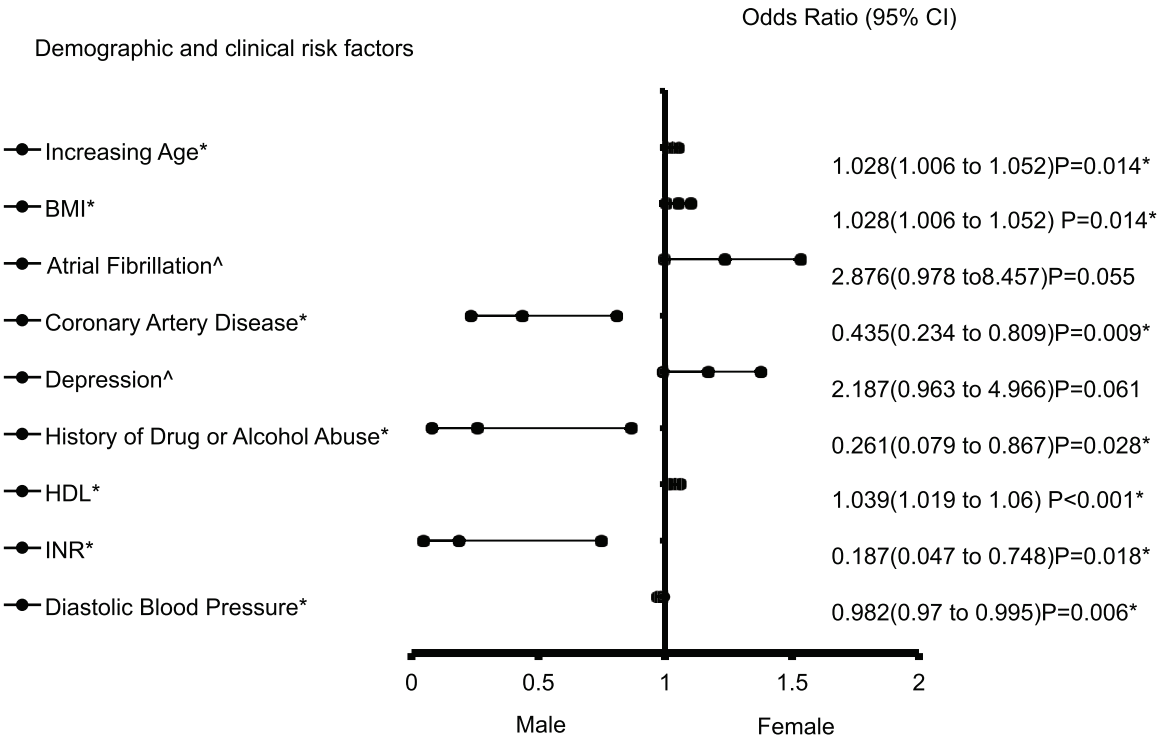

Figure 5. Forest plot representation of clinical factors that were associated with AIS population with high total cholesterol (≥240 mg/dl). Adjusted OR < 1 denote factors that are associated with being men while OR > 1 denote factors that are associated with being women. Hosmer-Lemeshow test ($P = .942$), Cox & Snell ($R^2 = .208$). The overall classified percentage of 73.3% was applied to check for fitness of the logistic regression model. *Indicates statistical significance ($P < .05$) with a 95% confidence interval.

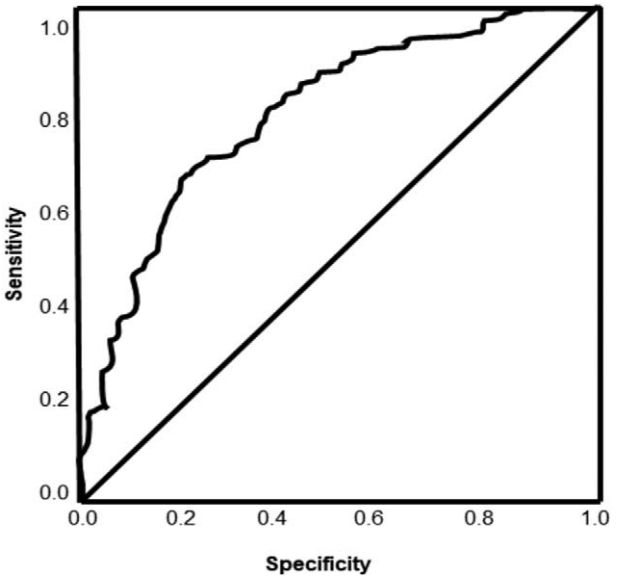

Figure 6. ROC curve for the predictive power of the regression model for AIS population with high total cholesterol (≥240 mg/dl). Higher area under the curve (AUC) values in ROC analysis indicate better discrimination of the score for the measured outcome. Classification table (overall correctly classified percentage = 73.3%) and area under the ROC curve (AUC = 0.785, 0.733–0.836) were applied to check model fitness.

stroke prevention.[27] Recent studies indicate that the reduction of LDL-C brings about a risk reduction for all strokes, including ischemic stroke.[55] While several studies have shown that dyslipidemia is associated traditionally with menopause is more associated with aging rather than by dysfunction of the ovaries,[27,38,56] future studies on the information about LDL-C in male and female ischemic stroke patients are necessary to elucidate the underlying physiological modulators of plasma lipid metabolism responsible for higher HDL-C expression and LDL-C in women AIS patients compared with men.

As discussed above, gender medicine emphasizes the importance of understanding physiological bases in the disparities observed in high total cholesterol in men and women[57,58] AIS patients. It is also important to understand other factors that could contribute to the observed disparities. Although the cross-sectional nature of our analysis does not allow us to determine the causal relationships or mechanisms underlying the observed gender-related disparities in total cholesterol, several explanations could be considered. Therefore, it is possible that despite similarity in prescriptions to reduce high total cholesterol levels, women may be less adherent to treatments[59,60] or that a treatment prejudice in favor of men exists. It is possible that in the latter, men AIS with high total cholesterol may be provided with better therapies or respond better to same therapies.[27,61] In general, women may also be presented with more social barriers and a reduced understanding of major risks of their high total cholesterol even prior to the onset of stroke, when compared with men. This low insight could be worsened by the occurrence of stress due to increasing work activities.[62] The aforementioned factors could result in a lower adherence to treatment in women, and this is supported by another study.[63] While sex-specific differences in the pharmacokinetics and pharmacodynamics of drugs are not very clear,[59,64] it is also possible that the higher total cholesterol could be attributed to worse lipid profiles reported in women compared with men,[65,66] and therefore disparities in demographic and clinical risk factors could also result in a gender-specific higher total cholesterol in AIS. Therefore, a prompt initiation of tailored prevention strategies to reduce a gender-specific higher total cholesterol in ischemic stroke patients. It has been shown a significant amount of ischemic events in male or female patients with ischemic stroke may be prevented through the use of an all-inclusive approach that includes dietary modification, exercise, effective strategies including the use of statins.[67] From a historical perspective, statin therapy in the prevention of cardiovascular disease is well documented in the literature[34,68] and supported by many guidelines. Precisely, the AHA guideline recommends the use of statins to reduce the risk of stroke.[69] Possible adverse events that have been associated with statin therapy are myopathy and hemorrhagic stroke.[23] Therefore, a more accurate understanding of the effectiveness and safety of different statins can be helpful in reducing a gender-specific higher total cholesterol. Therefore, understanding the different factors that impact men and women stroke populations is vital to promoting gender specific changes and this study is a step that provides information that can result in improved and better outcomes for patients.

The current study has strengths and limitations. Using a large hospital-based database and a robust statistical approach provided useful results. However, this is a single institution study, the results cannot be generalized to all populations. The retrospective nature introduces the tendency for selection bias that could have affected the selection of patients. We do not have data on the use of statins in these populations and we could not determine levels of treatment. However, despite these limitations, the strengths of this study stem from the fact that the registry used is a large stroke center in the state designed to monitor quality treatment. Therefore, this study is equipped to determine characteristics that were common between cohorts of women stratified by cholesterol levels. This study reveals a gender-related difference in demographic and clinical factors in AIS with different levels of cholesterol.

5. Conclusion

Our current results agree with the findings of the different studies, indicating a higher total cholesterol levels in women, despite similarities in the use of specific therapies. In addition, existing findings were advanced by showing that total high HDL-C was significantly elevated in the women compared to men AIS patients and that there are disparities in the clinical risk factors associated with total cholesterol levels in women compared to men AIS patients. These findings suggest the importance of considering specific gender-related therapeutic actions in treatment and management of AIS with history of total high HDL-C levels.

Acknowledgments

We thank the stroke unit of PRISMA Health-Upstate for helping in the data collection.

Author contributions

LB, NP, and TIN designed the concept, experiment and data analysis, while TS, LTR and JFE critically revised the drafts, interpreted the results, read and approved the last version of this manuscript.

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