Neurology Asia 2021; 26(4) : 649 – 655

ORIGINAL ARTICLES

Association between gallstone disease and ischemic stroke in Korea

Eun Sun Gill, Young Jin Jeong, Junyong Lee

Department of Family Medicine, Veterans Health Service Medical Center, Seoul, Republic of Korea

Abstract

Background & Objectives: In Korea, stroke incidence is projected to rise due to the rapid aging of the Korean population. Additionally, gallstone disease incidence is increasing in Korea, due to dietary and westernized lifestyle. In this cross-sectional study, we investigated the association between gallstone disease and ischemic stroke in Korea. *Methods*: We included 566 patients aged 40–89 years who underwent abdominal ultrasound or abdominal computed tomography at the VHS Medical Center between January 2008 and December 2010. Patient records were reviewed for the presence of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, obstructive coronary artery disease, and smoking history. The associations between risk factors, including gallstone disease, and ischemic stroke were analyzed using Pearson's chi-square tests. Multiple logistic regression analysis was performed with age, sex, smoking history, hypertension, obstructive coronary artery disease, and atrial fibrillation as covariates. *Results*: Age, sex, hypertension, obstructive coronary artery disease, atrial fibrillation, and smoking history were identified as significant risk factors for ischemic stroke (p-value < 0.05). Gallstone disease demonstrated an unadjusted odds ratio for ischemic stroke of 2.171 (95% confidence interval, 1.264–3.729); after adjustment for risk factors, the odds ratio was 2.015 (95% confidence interval, 1.151–3.528). *Conclusion*: In Korean patients, gallstone disease and ischemic stroke are correlated. Despite an unclear causality, the risk for ischemic stroke is significantly increased in patients with gallstone disease, even after adjusting for various confounders. Clinicians should be aware of the possibility of ischemic stroke in patients with gallstone disease, and should manage and educate patients accordingly.

Keywords: Cholelithiasis, gallstones, ischemic stroke, risk

INTRODUCTION

Stroke is a leading cause of death along with ischemic heart diseases worldwide and a major disease that may cause a severe disability.[1] In 2015 in Korea, the direct costs of strokes were 1.68 trillion Korean Won (KRW), including 1.11 trillion KRW for ischemic strokes, and compared to 2011, the direct costs for all strokes and ischemic stroke had increased by 29.6%, 36.2%, and 27.9%, respectively.[2] According to a 2018 Statistics Korea report, stroke accounts for 7.7% of all deaths in South Korea, and is ranked as the fourth leading cause of death following cancer, heart disease, and pneumonia.[3] The incidence of stroke is projected to rise further as a result of the rapid population aging of Korean society, with an estimated 350,000 new stroke cases annually by 2030.[4] Despite revolutionary advances in medicine and active research on stroke, a substantial number of patients still suffer from stroke.

Gallstone disease is particularly common in western societies[5], with a prevalence of 10%–15%[6], and in the USA, 300,000 patients undergo cholecystectomy due to gallstone disease every year.[7] Although there is no available data on the overall prevalence of gallstone disease in the Korean population, the prevalence reported by hospitals ranges from 3%–5%, which is lower than that in western countries.[8] However, growing adoption of a westernized lifestyle in Korea has led to an increase in the incidence of gallstone disease, from 127,000 in 2012 to 163,000 in 2017, showing an average annual increase rate of 5.1%.[9]

Address correspondence to: Young Jin Jeong, PhD, Department of Family Medicine, Veterans Health Service Medical Center, 53 Jinhwangdo-ro 61-gil, Gangdong-gu, Seoul 05368, Republic of Korea. Tel: +82-2-2225-1291, E-mail: kj1227@korea.com

Date of Submission: 2 January 2021; Date of Acceptance: 9 October 2021

https://doi.org/10.54029/2021yjc

Stroke and gallstone disease share risk factors, such as age, obesity, diabetes mellitus (DM), dyslipidemia, and alcohol drinking, and also share aspects of pathogenesis.[10,11] From this perspective, the two conditions are thought to be associated, and although several studies have investigated the relationship, they have had some limitations.[12-14] First, most previous studies classified stroke based on the International Classification of Disease (ICD) codes using insurance claims data, but the validity of ICD codes as a means for stroke classification needs to be established. ICD codes are often inaccurately entered, depending on the level of knowledge and experience of the healthcare provider.[15] In fact, Shima *et al*[16]. reported that the positive-predictive value of ICD codes for ischemic stroke was only 31.0%. Second, previous studies diagnosed gallstone disease based on self-reported questionnaires and ICD codes, but 80%–90% of gallstone disease are asymptomatic, and most cases are accidentally discovered during routine examination.[17-19] Thus, it is highly likely that asymptomatic gallstone disease cases were not included in previous studies, which would have undermined the accuracy of their analysis of the association between gallstone disease and stroke. Finally, previous studies were all conducted outside of Korea[12-14], and there is a paucity of studies on the association between gallstone disease and ischemic stroke in Korea.

Therefore, this study aimed to address the limitations of existing studies and to gain a better understanding of the association between gallstone disease and ischemic stroke by classifying and analyzing clinically diagnosed gallstone disease and ischemic stroke based on imaging data and medical records, in Korea.

METHODS

Study population and methods

In this retrospective cross-sectional study, we reviewed the medical records of 2,915 patients aged 40–89 years who had undergone abdominal ultrasound or abdominal computed tomography (CT) between January 2008 and December 2010 at the VHS Medical Center, followed by brain CT or brain magnetic resonance imaging (MRI) before November 2016. Of these patients, those with a history of cancer (n = 1,359), cholecystectomy (n = 201), stroke (n = 632), traumatic brain hemorrhage (n = 67), and brain tumor (n = 2), patients without imaging data (n = 14), and patients with missing data (n = 77) were excluded, resulting in a total of 566 patients for analysis (Figure 1).

Diagnosis of gallstone disease was defined as a radiologist's diagnosis of gallstone disease on abdominal ultrasound or abdominal CT, and ischemic stroke was defined as the presence of neurological symptoms in medical records and a radiologist's diagnosis of ischemic stroke based on brain CT or brain MRI taken 24 hours after symptom onset.

Factors such as hypertension (HTN), DM, dyslipidemia, atrial fibrillation (AF), obstructive coronary artery disease (OCAD), and smoking history were obtained by medical record review by a single researcher. HTN was defined as records

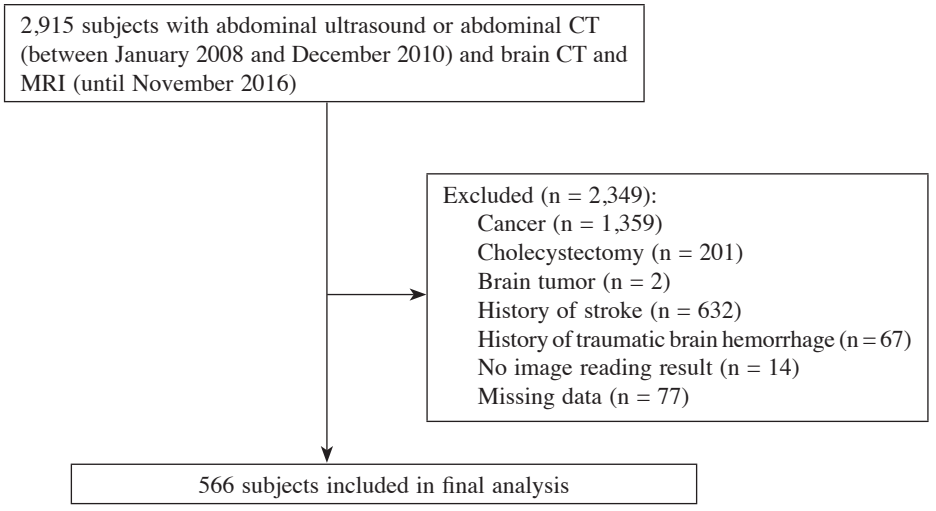

Figure 1. Criteria for selection of research subjects

of HTN or use of antihypertensive drugs in the patient's medical records. DM was defined as records of DM or use of oral glucose-lowering drugs or insulin, or the satisfaction of one of the diagnostic criteria presented in the 2015 Guidelines for the Care of DM published by the Korean Diabetes Association.[20] Dyslipidemia was defined as a record of dyslipidemia, use of dyslipidemia medications, or one or more of the following findings in blood tests: total cholesterol (TC) ≥ 240 mg/dL, triglyceride (TG) ≥ 200 mg/dL, low-density lipoprotein-cholesterol (LDL-C) ≥ 160 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL.[21] AF was defined as records of AF in the medical records or a researcher's determination of AF based on electrocardiogram (ECG) analysis. OCAD was defined as ≥ 50% coronary artery stenosis or records of percutaneous coronary artery intervention (PCI) or coronary artery bypass graft (CABG).[22] Past or current smokers were defined as smokers, and patients with no smoking history were defined as nonsmokers.

The protocol of this study was approved by the Institutional Review Board at the VHS Medical Center (IRB File No. 2017-04-004), who also waived the need for obtaining informed patient consent for this study.

Statistical analysis

The association between risk factors, including gallstone disease and ischemic stroke, was analyzed using Pearson's chi-square test. Multiple logistic regression analysis was performed, with age, sex, smoking history, HTN, OCAD, and AF, which were statistically significant in the χ^2 test, as covariates. The odds ratio (OR) and confidence interval (CI) of each risk factor, including gallstone disease, for ischemic stroke were computed. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS/WIN software ver. 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

General characteristics

The general characteristics of the patients included in the study are summarized in Table 1. Of the participants, 56.5% were between the ages of 65–89 years, and 71.6% were men. As shown in Table 1, among the various comorbidities examined, HTN and dyslipidemia were the most prevalent.

Prevalence of ischemic stroke by factor

The prevalence of ischemic stroke was significantly higher in smokers, males, and the 65–89-year age group. The prevalence of ischemic stroke was also significantly higher in individuals with HTN, AF, OCAD, and gallstone disease (Table 2).

Odds ratios of risk factors for ischemic stroke

Logistic regression was performed with age, sex, HTN, OCAD, AF, and smoking history as covariates, as they were shown to be significantly associated with stroke in univariate analyses. Table 3 displays the ORs for ischemic stroke before and after adjustment for each of these factors. After adjustment, the OR of the 65–89-year age group for ischemic stroke was 1.903 (95% CI, 1.143–3.169) and that of gallstone disease was 2.015 (95% CI, 1.151–3.528). The remaining factors were not significant after adjustment.

DISCUSSION

In this study, we examined the association between gallstone disease and ischemic stroke by reviewing the imaging data and medical records of 566 patients. The prevalence of ischemic stroke was significantly higher in the older (65–89 years) group as well as in individuals with HTN, AF, OCAD, and gallstone disease. The OR of gallstone disease for ischemic stroke, even after adjustment for other risk factors, was significantly increased.

Our study included a greater percentage of male subjects as well as a higher percentage of older adults (65–89 years). The demographics were largely due to the nature of the veterans hospital, which services the recipients of the Korean National Merit—a population that features a higher percentage of male and older patients. While we found an association between gallstone disease and ischemic stroke in our study population, gallstone disease is reportedly more common in women[10], which may have influenced our results.

The prevalence of HTN, AF, and OCAD, which were statistically significant risk factors, were 61.1%, 5.8%, and 12.0%, respectively. The previously reported prevalence of HTN (33.3%)[23], AF (1.53%)[24], and physicians' diagnosis of ischemic heart disease (1.9%) in the Korean population are lower than those found in our study.[25] This may be because the present study only enrolled patients aged 40–89 years from a single hospital, whose population composition differs from that of the general population. Additionally,

Table 1: Baseline characteristics of study subjects (N = 566)

Variable	n (%)
Age (years)	66.5 ± 8.99
40 – 64	246 (43.5)
65 – 89	320 (56.5)
Sex	
Male	405 (71.6)
Female	161 (28.4)
Medical history	
HTN	
Yes	346 (61.1)
No	220 (38.9)
DM	
Yes	200 (35.3)
No	366 (64.7)
Dyslipidemia	
Yes	314 (55.5)
No	252 (44.5)
AF	
Yes	33 (5.8)
No	533 (94.2)
OCAD	
Yes	68 (12.0)
No	498 (88.0)
Smoking history	
Yes	241 (42.6)
No	325 (57.4)
Gallstone disease	
Yes	90 (15.9)
No	476 (84.1)
Ischemic stroke	
Yes	88 (15.5)
No	478 (84.5)

Values are presented as mean ± standard deviation or number (%).
Abbreviations: HTN, hypertension; DM, diabetes mellitus; AF, atrial fibrillation; OCAD, obstructive coronary artery disease.

we only enrolled patients who had undergone both abdominal and brain imaging, leaving the study vulnerable to a selection bias. In addition, a large number of patients with a history of cancer and stroke were excluded from this study, which may have further contributed to the selection bias.

However, gallstone disease and ischemic stroke were significantly correlated even after adjusting for age, sex, HTN, AF, and OCAD; thus, these factors would not have had an impact on the relationship between the two factors. Our results were consistent with previous reports that have shown an association between stroke and gallstone disease. A study by Wei *et al*.[13] showed that the hazard ratio for ischemic stroke in patients with gallstone disease was 1.28 (95% CI, 1.25–1.31) even after adjusting for age, sex, and comorbidities. Furthermore, Olaiya *et al*.[22] also reported an OR of gallstone disease for stroke of 1.15 (95% CI, 1.01–1.32). Studies examining gallstone disease and heart disease have also shown similar correlations. Wirth *et al*.[14] reported a risk ratio for myocardial infarction and stroke of 1.24 (95% CI, 1.02–1.50) in individuals with gallstone disease, while Lv *et al*.[26] suggested that gallstone disease was associated with a higher

Table 2: Associated factors for ischemic stroke in the study subjects (N = 566)

Variable	Ischemic stroke		P value[a]
	Yes (n = 88)	No (n = 478)	
	n (%)	n (%)	
Age (years)			
40 – 64	25 (10.2)	221 (89.8)	0.002
65 – 89	63 (19.7)	257 (80.3)	
Sex			
Male	74 (18.3)	331 (81.7)	0.005
Female	14 (8.7)	147 (91.3)	
Medical history			
HTN			
Yes	63 (18.2)	283 (81.8)	0.028
No	25 (11.4)	195 (88.6)	
DM			
Yes	36 (18.0)	164 (82.0)	0.234
No	52 (14.2)	314 (85.8)	
Dyslipidemia			
Yes	45 (14.3)	269 (85.7)	0.373
No	43 (17.1)	209 (82.9)	
AF			
Yes	10 (30.3)	23 (69.7)	0.016
No	78 (14.6)	455 (85.4)	
OCAD			
Yes	18 (26.5)	50 (73.5)	0.008
No	70 (14.1)	428 (85.9)	
Smoking history			
Yes	47 (19.5)	194 (80.5)	0.025
No	41 (12.6)	284 (87.4)	
Gallstone disease			
Yes	23 (25.6)	67 (74.4)	0.004
No	65 (13.7)	411 (86.3)	

Values are presented as number(%), [a]by Pearson Chi-square test.
Abbreviations: HTN, hypertension; DM, diabetes mellitus; AF, atrial fibrillation; OCAD, obstructive coronary artery disease.

Table 3: Odds ratio and 95% confidence interval of risk factors for ischemic stroke

Variable	Unadjusted		Adjusted[a]	
	OR	95% CI	OR	95% CI
Age (65 – 89 years)	2.167	1.318 – 3.562	1.903	1.143 – 3.169
Male	2.347	1.284 – 4.292	1.691	0.845 – 3.386
HTN	1.736	1.055 – 2.857	1.462	0.865 – 2.470
AF	2.536	1.162 – 5.534	2.108	0.935 – 4.754
OCAD	2.201	1.214 – 3.991	1.645	0.875 – 3.094
Smoking history	1.678	1.063 – 2.650	1.327	0.783 – 2.249
Gallstone disease	2.171	1.264 – 3.729	2.015	1.151 – 3.528

Values are presented as odds ratio (95% confidence interval).
[a]After adjusting for age, sex, HTN, AF, OCAD, Smoking history, Gallstone disease using logistic regression analysis.
Abbreviations: OR, odds ratio; CI, confidence interval; HTN, hypertension; AF, atrial fibrillation; OCAD, obstructive coronary artery disease.

risk of ischemic heart disease.

In this study, dyslipidemia was not associated with ischemic stroke. In fact, previous studies reported that high LDL-C and low HDL-C, as opposed to TC and TG, elevate the risk of ischemic stroke.[27] However, we comprehensively considered TC, LDL-C, HDL-C, and TG to define dyslipidemia in this study, which may have contributed to the absence of association.

The association between ischemic stroke and gallstone disease might arise from the similar pathophysiological mechanisms of these two conditions. First, accumulation of cholesterol contributes to the onset of both diseases, where elevated cholesterol levels induce oversaturation of cholesterol in the bile, and nucleation in the bile and reduced gallbladder motility lead to the formation of gallstones.[28] Ischemic stroke is also caused when atherosclerotic plaques formed as a result of intravascular accumulation of cholesterol, which leads to thrombosis and thus provokes cerebral circulatory disturbance.[29] Second, common genetic factors are involved in the onset of both diseases. One of these genetic factors involves a gene related to cholesterol metabolism, i.e., the ApoE ε4 allele. This genetic factor is linked to high levels of LDL-C, TC, and non-HDL-C[30], and previous studies confirmed that the ApoE ε4 allele is both a risk factor for gallstone disease and a factor involved in ischemic stroke.[31,32]

This study had several limitations. First, this was a cross-sectional study, and thus causality cannot be determined. Subsequently, prospective studies should be conducted to determine the nature of this causality by examining whether ischemic stroke occurs in patients with gallstone disease. Second, gallstone disease can be broadly divided into cholesterol and pigment gallstones, depending on their formation mechanisms, but we could not examine the association of each of these types of gallstone disease with ischemic stroke. However, based on a Korean report of gallstone composition analysis that showed an elevated prevalence of cholesterol gallstones (60%–70% of all cases)[33], and given that a westernized lifestyle would have further increased the percentage of cholesterol gallstones[34], this is believed to have had minimal impact on our findings. Third, although our results were adjusted for age and sex, the study population had a larger proportion of older adults and was predominantly male (M:F ratio of 3:2), which could affect the generalizability of our findings.

Despite these limitations, this study was significant in the following respects. Although previous studies utilized ICD codes in the diagnosis of gallstone disease and stroke, without verifying the accuracy of the codes[12,13], ICD codes are mainly used for insurance claims purposes and may be inaccurately entered depending on the level of knowledge and proficiency of the healthcare provider. To address this, one researcher in our study meticulously reviewed patients' medical records to enhance the diagnostic accuracy of gallstone disease and stroke in this study. Another significance strength of this study is that we included asymptomatic cases in the analysis of the association between gallstone disease and ischemic stroke, thereby improving the accuracy of the analysis, as asymptomatic gallstone disease accounts for 80%–90% of all cases.[17-19]

In this study, gallstone disease was correlated with ischemic stroke. Although the causal link is unclear, the risk for ischemic stroke was significantly increased in patients with gallstone disease, even after adjusting for various risk factors. Clinicians should be aware of the possibility of ischemic stroke in patients with gallstone disease, and should manage patients accordingly, and educate them about stroke risk factors.

ACKNOWLEDGEMENTS

We would like to thank Editage (www.editage.co.kr) for English language editing.

DISCLOSURE

Financial support: This study was funded by a grant from the VHS Veterans Medical Research Institute under the designated research number VHSMC18005.

Conflicts of interest: None

REFERENCES

1. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. *Circ Res* 2017;120(3):439-48.
2. Kim JY, Kang K, Kang J, *et al*. Executive summary of stroke statistics in Korea 2018: A Report from the Epidemiology Research Council of the Korean Stroke Society. *J Stroke* 2019;21(1):42-59.
3. Statistics Korea. Annual report on the causes of death statistics 2018 [Internet]. Daejeon: Statistics Korea; 2019 [updated 2019 Sep 23; cited 2021 Jan 1]. Available from: http://kostat.go.kr/assist/synap/preview/skin/doc.html?fn=synapview377606_1&rs=/assist/synap/preview

4. Statistics Korea. Population projections and summary indicators (Korea). [Internet] Daejeon: Statistics Korea; 2019[updated 2019 Mar 28; cited 2021 Jan 1]. Available from: http://kosis.kr/statHtml/statHtml.do?orgId=101&tblId=DT_1BPA002&conn_path=I2&language=en
5. Diehl AK. Cholelithiasis and the insulin resistance syndrome. *Hepatology* 2000;31(2):528-30.
6. Warttig S, Ward S, Rogers G. Guideline Development Group. Diagnosis and management of gallstone disease: summary of NICE guidance. *BMJ* 2014;349:g6241.
7. Hassler KR, Collins JT, Jones MW. Laparoscopic cholecystectomy [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 January [updated 2021 Sep 28; cited 2021 Jan 1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448145/
8. Lee JK, Rhee PL, Lee JH, *et al*. Prevalence and risk factors of gallstone in health screening people. *Korean J Gastroenterol* 1997;29(1):85-92.
9. National Health Insurance Service. Among the patients with cholelithiasis on my body who showed no subjective symptoms, 70.3% of all patients are over 50 years [Internet]. Wonju: National Health Insurance Service; 2018 [updated 2018 Nov 14; cited 2021 Jan 1]. Available from: https://www.nhis.or.kr/
10. Conte D FM, Giunta M, Conti CB. Gallstones and liver disease: An overview. *J Gastrointestin Liver Dis* 2011;20(1):9-11.
11. Meschia JF, Bushnell C, Boden-Albala B, *et al*. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(12):3754-832.
12. Olaiya MT, Chiou HY, Jeng JS, Lien LM, Hsieh FI. Significantly increased risk of cardiovascular disease among patients with gallstone disease: a population-based cohort study. *PLoS One* 2013;8(10):e76448.
13. Wei CY, Chung TC, Chen CH, *et al*. Gallstone disease and the risk of stroke: a nationwide population-based study. *J Stroke Cerebrovasc Dis* 2014;23(7):1813-20.
14. Wirth J, di Giuseppe R, Wientzek A, *et al*. Presence of gallstones and the risk of cardiovascular diseases: The EPIC-Germany cohort study. *Eur J Prev Cardiol* 2015;22(3):326-34.
15. O'malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: ICD code accuracy. *Health Services Research* 2005;40(5p2):1620-39.
16. Shima D, Ii Y, Higa S, *et al*. Validation of algorithms to identify acute myocardial infarction, ischemic stroke, and hemorrhagic stroke cases from Japanese claims database. *Value in Health* 2018;21:S95.
17. Angelico F, Del Ben M, Barbato A, Conti R, Urbinati G. Ten-year incidence and natural history of gallstone disease in a rural population of women in central Italy. The Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO). *Ital J Gastroenterol Hepatol* 1997;29(3):249.
18. Barbara L, Sama C, Labate AMM, *et al*. A population study on the prevalence of gallstone disease: the Sirmione Study. *Hepatology* 1987;7(5):913-7.
19. Berger MY, Van Der Velden JJIM, Lijmer JG, De Kort H, Prins A, Bohnen AM. Abdominal symptoms: do they predict gallstones?: a systematic review. *Scand J Gastroenterol* 2000;35(1):70-6.
20. The Journal of Korean Diabetes. 2015 Treatment Guidelines for Diabetes (5th edition). Seoul; 2015.
21. Committee for the Korean Guidelines for the Management of Dyslipidemia. 2015 Korean Guidelines for the Management of Dyslipidemia: Executive Summary (English Translation). *Korean Circ J* 2016;46(3):275-306.
22. Rosenthal RL. The 50% coronary stenosis. *Am J Cardiol* 2015;115(8):1162-5.
23. Korea Disease Control and Prevention Agency. Hypertension prevalence trend(2018). [Internet] Cheongju: Korea Disease Control and Prevention Agency; 2018 [updated 2020 Feb 11; cited 2021 Jan 1]. Available from: https://kosis.kr/statHtml/statHtml.do?orgId=117&tblId=DT_11702_N105
24. Kim D, Yang PS, Jang E, *et al*. 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. *Am Heart J* 2018;202:20-6.
25. Korea Disease Control and Prevention Agency. Angina or myocardial infarction physician diagnosis experience rate (2018). Cheongju: Korea Disease Control and Prevention Agency; 2019 [cited 2021 Jan 1]. Available from: https://health.kdca.go.kr/healthinfo/biz/pblcVis/details.do?ctgrSn=29
26. Lv J, Qi L, Yu C, *et al*. Gallstone disease and the risk of ischemic heart disease. *Arterioscler Thromb Vasc Biol* 2015;35(10):2232-7.
27. Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP. Dyslipidemia as a risk factor for ischemic stroke. *Curr Top Med Chem* 2009;9(14):1291-7.
28. Joo KR. Pathophysiology of gallstone. *Korean J Med* 2008;75:607-15.
29. Corrigan ML, Escuro AA, Kirby DF. Handbook of clinical nutrition and stroke. 1st ed. Totowa, NJ: Humana Press, 2013: 1-310.
30. Zhao SF, Wang AM, Yu XJ, Wang LL, Xu XN, Shi GJ. Association between gallstone and cardio-cerebrovascular disease: Systematic review and meta-analysis. *Exp Ther Med* 2019;17(4):3092-100.
31. Chen C, Hu Z. ApoE polymorphisms and the risk of different subtypes of stroke in the Chinese population: a comprehensive Meta-analysis. *Cerebrovasc Dis* 2016;41(3-4):119-38.
32. Xue P, Niu WQ, Jiang ZY, Zheng MH, Fei J. A meta-analysis of apolipoprotein E gene ε2/ε3/ε4 polymorphism for gallbladder stone disease. *PLoS One* 2012;7(9):e45849.
33. Moon SH. An approach to patients with symptomatic cholelithiasis based on degree of probability for choledocholithiasis. *The Korean journal of medicine* 2017;92(2):150-4.
34. Kim J, Lee K. Relationship between metabolic syndrome and gallbladder stone. *Korean J Fam Med* 2009;30(8):610-6.