Investigating Long-Term Risk of Aortic Aneurysm and Dissection from Fluoroquinolones and the Key Contributing Factors Using Machine Learning Methods

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Article

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Abstract

The connection between fluoroquinolones and severe heart conditions, such as aortic aneurysm (AA) and aortic dissection (AD), has been acknowledged, but the full extent of long-term risks remains uncertain. Addressing this knowledge deficit, a retrospective cohort study was conducted in Taiwan, utilizing data from the National Health Insurance Research Database spanning from 2004 to 2010, with follow-up lasting until 2019. The study included 232,552 people who took fluoroquinolones and the same number of people who didn't, matched for age, sex, and index year. The Cox regression model was enlisted to calculate the hazard ratio (HR) for AA/AD onset. Additionally, five machine learning algorithms assisted in pinpointing critical determinants for AA/AD among those with fluoroquinolones. Intriguingly, within the longest follow-up duration of 16 years, exposed patients presented with a markedly higher incidence of AA/AD. After adjusting for multiple factors, exposure to fluoroquinolones was linked to a higher risk of AA/AD (HR 1.62). Machine learning identified ten factors that significantly affected AA/AD risk in those exposed. These results show a 62% increase in long-term AA/AD risk after fluoroquinolone use, highlighting the need for healthcare professionals to carefully consider prescribing these antibiotics due to the risks and factors involved.

Introduction

Fluoroquinolone, a class of broad-spectrum antibacterial drugs effective against a variety of gram-negative and gram-positive pathogens, have been widely used for several decades [1].

Despite their efficacy in treating a range of infections, these agents have been associated with several safety concerns, including tendinopathy, QTc prolongation, and, potentially, adverse effects on collagen and other connective tissue structures [2–5]. In recent years, concerns have extended to the potential long-term risk of serious vascular complications, particularly aortic aneurysm (AA) and aortic dissection (AD), the latter being catastrophic events associated with high mortality rates[6,7].

Aortic aneurysm, a condition characterized by an abnormal focal dilation of the arterial wall, and its extreme sequel, dissection, pose significant health burdens due to their asymptomatic nature and potential for sudden, fatal rupture [8,9]. Emerging epidemiological evidence suggests that fluoroquinolones may contribute to these disorders by disrupting the integrity of collagen within the aortic wall, thus underlining a pressing need for a comprehensive review of their long-term vascular risks [10–12]. The concern was first raised when laboratory studies highlighted the capacity of fluoroquinolones to upregulate matrix metalloproteinases (MMPs), enzymes responsible for the degradation of collagen and elastin, which play a crucial role in maintaining the structural integrity of the aorta[13,14]. This biochemical mechanism provided a plausible link between fluoroquinolone use and increased risk of AA or AD, prompting observational studies and subsequent pharmacovigilance efforts.

In 2008, the United States Food and Drug Administration issued a black box warning for fluoroquinolones based on post-marketing surveillance data indicating their association with post-treatment tendonitis and

tendon rupture. Subsequent studies demonstrated the association of fluoroquinolones with increased risk of AA and AD[15,16]. In population-based cohort studies in Canada and Sweden, Daneman et al.[17] and Pasternak et al.[11] found that fluoroquinolones exposure was associated with greater risk of AA (hazard ratio [HR] 2.24, 95% confidence interval [CI] 2.02–2.49) and AA/AD (HR 1.66, 95%CI 1.12–2.46), respectively. These findings are supported by several case-control studies NHIRD [10,12,18–20].

Although previous studies have identified a potential association between AA/AD and fluoroquinolone exposure, there may be limitations regarding the long-term follow-up of patients taking fluoroquinolones. Our study embarked on a comprehensive exploration of the potential link between fluoroquinolone exposure and the development of aortic aneurysm (AA) and aortic dissection (AD) over an extended timeline. Utilizing the extensive data available from the National Health Insurance Research Database (NHIRD), our objective was to thoroughly assess the connection between fluoroquinolone use and the risk of AA/AD in a real-world context. Moreover, we aimed to identify predictive markers that could be leveraged in clinical settings to assess the risk of AA/AD in patients prescribed fluoroquinolones. To accomplish this, we employed advanced machine learning techniques to analyze the data, aiming to provide clinically relevant insights that could inform safer prescribing practices and enhance patient care.

Materials and Methods

Data sources

Our study was designed as a retrospective cohort, utilizing the extensive information available from the NHIRD. The NHIRD, since its establishment in 1998, has been an exhaustive resource, encompassing coverage for a sweeping majority of the population in Taiwan, accounting for nearly 99 percent[21]. This expansive database holds a wealth of data points covering different aspects of healthcare services such as hospital stays, appointments with medical professionals in outpatient settings, along with a plethora of other healthcare-related information. It encompasses detailed records of surgical procedures undergone by individuals, the variety of medications prescribed, and the specific disease diagnosis codes assigned to patients' conditions. These diagnostic codes are formulated in alignment with the globally recognized International Classification of Diseases Ninth Revision Clinical Modification, commonly abbreviated as International Classification of Diseases Ninth Revision Clinical Modification [22]. Before releasing the data analysis, Taiwan's Ministry of Health and Welfare (MOHW) took important measures to protect the privacy of people represented in our study. The MOHW carefully anonymized the records of all claimants, stripping the dataset of any personal identifiers effectively.

In preparation for our in-depth analysis, we ensured that all personal identifiers within the beneficiary claim records had been removed, rendering the data deidentified for the protection of personal privacy. Therefore, the Institutional Review Board of Shin-Kong Wu Ho-Su Memorial Hospital, responsible for overseeing the ethical aspects of our research, authorized the waiver of informed consent. This approval validated our approach and granted us permission to proceed with our investigation without requiring

direct consent from the individuals in the dataset (protocol No.: 20200720R). All methods in this study were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

Study population and baseline variables

The database we used for our study included information from 2002 to 2019. Our attention was directed towards individuals who were registered between the dates of January 1, 2004, and December 31, 2010. Subsequently, we diligently observed their progress until the conclusion of the observation period on December 31, 2019.

Figure 1 illustrates the scheme for selecting patients in our study from 2004 to 2010. We had a group of patients who were exposed to fluoroquinolones. This group consisted of 232,552 individuals who were prescribed either oral fluoroquinolones (specifically ciprofloxacin, levofloxacin, moxifloxacin, and gemifloxacin) or intravenous fluoroquinolones (specifically ciprofloxacin, levofloxacin, and moxifloxacin) during a visit to the outpatient department or as part of a hospital admission. To identify patients with new onset conditions, we applied the following exclusion criteria: (1) patients who had received fluoroquinolones prescriptions prior to 2002–2003, (2) patients who had already been diagnosed with AA or AD in 2002–2003, (3) patients with missing information, and (4) patients under the age of 18. The index date of the group with fluoroquinolones exposure was one month after the initial medication of fluoroquinolones records.

To form a comparison group that hadn't been exposed to fluoroquinolones, we systematically paired individuals with counterparts from the group of those who did receive fluoroquinolones, ensuring that each match was made with a 1:1 ratio. This meticulous pairing process considered several important characteristics. Age, gender, and the specific year within the range of 2004 to 2010, also known as the index year, were the key factors considered to align the two groups as closely as possible. For the group that had not been exposed to fluoroquinolones, we assigned an index date that corresponded directly to the index date for their paired counterparts who had been exposed to the medication. This method allowed for consistent comparison across both groups.

Definition of variables

Three variable categories were included in the present study. The first category included those included in propensity score matching (index years, age, sex). The second category was composed of comorbidities including hypertension; hyperlipidemia; diabetes mellitus (DM); cirrhosis; chronic kidney disease; cerebrovascular disease; ischemic stroke; chronic obstructive pulmonary disease (COPD); coronary artery disease (CAD); asthma; genital tract infection (GTI), soft tissue and bone infection (STBI), and lower respiratory tract infections (LRTI); septicemia; and seizure disorder (Supplementary Table S1 online for codes of diseases). The third category was composed of medications including angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), beta-blockers, calcium channel blockers (CCB), insulin, nonsteroidal anti-inflammatory drugs (NSAID), diuretics, and oral and intravenous steroids (Supplementary Table S2 online for codes of medications).

Study outcomes

The main result of our study focused on patients who were admitted to the hospital for AA/AD, for which the specific codes used to identify these conditions are provided in further detail in Supplementary Table S1 online. The dataset was examined, starting from the index date, and continued until the specific endpoints were reached. This close examination was carried out up to the point at which the first instance of a new AA/AD diagnosis was identified, the occurrence of death from any cause, or until the preset conclusion of the observation period, which was determined to be December 31, 2019. The analysis concluded with whichever of these three events happened the earliest.

Statistical analysis

We presented all demographic results as percentages for categorical data and as means with standard deviations for continuous data. Categorical and continuous variables were compared using the chi-square and Student's *t* tests, respectively. To eliminate discrepancies between groups, propensity score matching with a 1:1 ratio between groups with/without fluoroquinolones exposure was used in subsequent analyses. Cox proportional regression models were used to estimate HRs with 95%CIs for AA/AD risk. The first model was a crude analysis and the second model incorporated additional adjustments for all the baseline confounders. We tested the proportional hazard assumption by schoenfeld residuals. A two-tail *P*-value less than .05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Moreover, feature selection was used to find the important features of AA/AD in patients with fluoroquinolones exposure, thereby excluding unimportant variables and improving the accuracy of machine learning models [23,24]. Feature selection models used in the present study were logistic regression (LGR), random forest (RF), classification and regression tree, multivariate adaptive regression splines (MARS), multivariate adaptive regression splines (CART), and extreme gradient boosting (eXGBoost). Since the algorithm used for each model was different, the selection process for each variable varied as well. To ensure fairness, this research averaged all the features generated by each model and ranked the scores from high to low. The variable with the highest average score is considered the most important, and so on (Supplementary Figure S1 online). The R software (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria) was used for feature selection.

Results

Baseline characteristics of patients

The distributions of age, sex, comorbidities, and medications of target population are presented in Table 1. Briefly, the rates of comorbidities were significantly higher in the group with fluoroquinolones exposure than in those without fluoroquinolones exposure and included hypertension (13.22% vs. 7.84%, *P*< .001), hyperlipidemia (30.95% vs. 24.02%, *P*< .001), DM (33.21% vs. 19.67%, *P*< .001), cirrhosis (5.37% vs.

1.83%, *P*< .001), chronic kidney disease (16.18% vs. 4.84%, *P*< .001), stroke (26.02% vs. 12.48%, *P*< .001), ischemic stroke (8.89% vs. 2.87%, *P*< .001), COPD (42.87% vs. 22.03%, *P*< .001), CAD (11.88% vs. 3.84%, *P*< .001), asthma (23.92% vs. 11.83%, *P*< .001), GTI (60.98% vs. 31.56%, *P*< .001), STBI (50.26% vs. 30.56%, *P*< .001), LRTI (49.59% vs. 21.79%, *P*< .001), septicemia (10.77% vs. 3.73%, *P*< .001), and seizure disorder (0.83% vs. 0.21%, *P*< .001). Similarly, the use rates of specific medications were significantly higher in the group with fluoroquinolones exposure than in those without fluoroquinolones exposure and included ACEI/ARB (12.11% vs. 7.82%, *P*< .001), beta-blockers (14.83% vs. 11.18%, *P*< .001), CCB (26.18% vs. 15.7%, *P*< .001), insulin (11.13% vs. 1.08%, *P*< .001), NSAID (46.81% vs. 31.64%, *P*< .001), diuretics (2.62% vs. 2.02%, *P*< .001), oral steroids (65.66% vs. 45.08%, *P*< .001), and intravenous steroids (54.29% vs. 23.62%, *P*< .001).

Table 1
Demographic and clinical characteristics of study population

Variables	fluoroquinolones exposure (n = 232,552)	Non- fluoroquinolones exposure (n = 232,552)	*p* value
Sex			
Male (%)	127,710 (54.92)	128,032 (55.06)	0.342
Female (%)	104,842 (45.08)	104,520 (44.94)	
Age, years	60.7±17.9	60.7±17.8	0.168
Index year			
2004 (%)	20,706 (8.90)	20,546 (8.84)	0.878
2005 (%)	24,510 (10.54)	24,343 (10.47)	
2006 (%)	29,181 (12.55)	29,068 (12.50)	
2007 (%)	33,787 (14.53)	33,786 (14.53)	
2008 (%)	36,164 (15.55)	36,208 (15.57)	
2009 (%)	40,278 (17.32)	40,398 (17.37)	
2010 (%)	47,926 (20.61)	48,203 (20.73)	
Comorbidities			
Hypertension (%)	30,750 (13.22)	18,242 (7.84)	< 0.001
Hyperlipidemia (%)	71,964 (30.95)	55,862 (24.02)	< 0.001
Diabetes mellitus (%)	77,219 (33.21)	45,748 (19.67)	< 0.001
Hepatobiliary disorders (%)	12,482 (5.37)	4,263 (1.83)	< 0.001
Kidney disease (%)	37,627 (16.18)	11,246 (4.84)	< 0.001
Cerebrovascular disease (%)	60,500 (26.02)	29,013 (12.48)	< 0.001
Ischemic stroke (%)	20,668 (8.89)	6,673 (2.87)	< 0.001
COPD (%)	99,688 (42.87)	51,241 (22.03)	< 0.001

Variables	fluoroquinolones exposure (n = 232,552)	Non- fluoroquinolones exposure (n = 232,552)	*p* value
Coronary artery disease (%)	27,626 (11.88)	8,935 (3.84)	< 0.001
Asthma (%)	55,627 (23.92)	27,521 (11.83)	< 0.001
GTI (%)	141,809 (60.98)	73,392 (31.56)	< 0.001
STBI (%)	116,885 (50.26)	71,071 (30.56)	< 0.001
LRTI (%)	115,318 (49.59)	50,667 (21.79)	< 0.001
Septicemia (%)	25,041 (10.77)	8,673 (3.73)	< 0.001
Seizure disorder (%)	1,928 (0.83)	487 (0.21)	< 0.001
Medications			
ACEI/ARB (%)	28,161 (12.11)	18,177 (7.82)	< 0.001
Beta-blockers (%)	34,484 (14.83)	25,998 (11.18)	< 0.001
Calcium channel blocker (%)	60,873 (26.18)	36,519 (15.7)	< 0.001
Insulin (%)	25,887 (11.13)	2,508 (1.08)	< 0.001
NSAIDs (%)	108,860 (46.81)	73,576 (31.64)	< 0.001
Diuretics (%)	6,094 (2.62)	4,698 (2.02)	< 0.001
Oral steroids (%)	152,699 (65.66)	104,839 (45.08)	< 0.001
Intravenous steroids (%)	126,251 (54.29)	54,918 (23.62)	< 0.001

Abbreviation: COPD, chronic obstructive pulmonary disease; GTI, genital tract infection; LRTI, lower respiratory tract infection; STBI, soft tissue and bone infection; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drug.

Risk factors for the development of AA/AD

Table 2shows the determinants of AA/AD in the study population. In multivariable analysis, in addition to fluoroquinolones (HR 1.61, 95%CI 1.45–1.78), old age (HR 2.21, 95%CI 1.55–3.14 for 40–55 years vs. <40 years; HR 9.39, 95%CI 6.83–12.92 for ≥ 55 years vs. <40 years), male sex (HR 2.47, 95%CI 2.23–2.74), hypertension (HR 1.14, 95%CI 1.02–1.28), DM (HR 0.75; 95%CI 0.68–0.83), cirrhosis (HR 0.75, 95%CI 0.57–0.97), cerebrovascular disease (HR 1.30, 95%CI 1.16–1.45), CAD (HR 1.50, 95 CI 1.16–1.93), asthma (HR 0.88, 95%CI 0.79–0.97), septicemia (HR 1.36, 95%CI 1.20–1.54), ACEI/ARB (HR 1.40, 95%CI 1.24–1.58), beta-blockers (HR 1.36, 95%CI 1.22–1.51), CCB (HR 1.59, 95%CI 1.44–1.75), insulin (HR 0.56, 95%CI 0.45–0.70), NSAIDs (HR 0.90, 95%CI 0.82–0.98), oral steroids (HR 1.75, 95%CI 1.56–1.96), and intravenous steroids (HR 4.29, 95%CI 3.82–4.81) were independently associated with the development of AA/AD.

Table 2
Multivariable adjusting Cox regression analysis to determine risk covariates for aortic dissection and aneurysm.

Characteristics		Aortic dissection and aneurysm	
		aHR (95%CI) *	*P*-value
FQs exposure vs. Non-FQs exposure		1.61 (1.45–1.78)	< 0.001
Age group, years	< 40 (reference)	1	< 0.001
	40–55	2.21 (1.55–3.14)	
	≥ 55	9.39 (6.83–12.92)	
Male vs. female		2.47 (2.23–2.74)	< 0.001
Comorbidities			
Hypertension		1.14 (1.02–1.28)	0.023
Hyperlipidemia		0.97 (0.89–1.07)	0.565
Hyperparathyroidism		0.84 (0.37–1.88)	0.669
Diabetes mellitus		0.75 (0.68–0.83)	< 0.001
Hepatobiliary disorders		0.75 (0.57–0.97)	0.031
Kidney disease		0.93 (0.73–1.17)	0.508
Cerebrovascular disease		1.30 (1.16–1.45)	< 0.001
Ischemic stroke		1.12 (0.95–1.31)	0.183
Chronic obstructive pulmonary disease		1.06 (0.96–1.17)	0.252
Coronary artery disease		1.50 (1.16–1.93)	0.001
Asthma		0.88 (0.79–0.97)	0.014
Genital tract infection		1.03 (0.93–1.13)	0.608
Soft tissue and bone infection		0.90 (0.82–0.98)	0.015
Lower respiratory tract infection		0.97 (0.88–1.07)	0.532
Septicemia		1.36 (1.20–1.54)	< 0.001
Seizure		0.50 (0.25–1.01)	0.052
Medications			
ACEI/ARB		1.40 (1.24–1.58)	< 0.001

* The full multivariable adjusting model included all baseline comorbidities and medications.

Characteristics	Aortic dissection and aneurysm	
	aHR (95%CI) *	*P*-value
Beta-blockers	1.36 (1.22–1.51)	< 0.001
Calcium channel blocker	1.59 (1.44–1.75)	< 0.001
Insulin	0.56 (0.45–0.70)	< 0.001
NSAIDs	0.90 (0.82–0.98)	0.018
Diuretics	0.82 (0.65–1.04)	0.101
Oral steroids	1.75 (1.56–1.96)	< 0.001
Intravenous steroids	4.29 (3.82–4.81)	< 0.001
* The full multivariable adjusting model included all baseline comorbidities and medications.		

Abbreviation: FQs, fluoroquinolones; CI, confidence interval; aHR, adjusted hazard ratio; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, non-steroidal anti-inflammatory drug.

Association of fluoroquinolones exposure with AA/AD

Over a longest 16-year follow-up period, the Kaplan-Meier plot in Fig. 2 reveals a significant difference in the occurrence of AA/AD events between groups exposed to fluoroquinolones and those not exposed (p < .001). Additionally, Table 3illustrates that we compared 1,389 patients who recently developed AA or AD and were exposed to fluoroquinolones to 675 patients who also recently developed AA or AD but were not exposed to fluoroquinolones. The rate of AA/AD was higher in the group exposed to fluoroquinolones compared to those not exposed (80 vs. 30 per 100,000 person-years).

Table 3
Comparison of the risk for aortic aneurysm and aortic dissection between patients with and without fluroquinolone exposure

Clinical outcome	FQs exposure (n = 232,552)		Non- FQs exposure (n = 232,552)		FQs exposure vs. Non- FQs exposure			
	Events	IR	Events	IR	Crude HR (95% CI)	P value	aHR* (95% CI)	P value
AA/AD	1389	80	675	30	2.39 (2.18–2.62)	< 0.001	1.61 (1.45–1.78)	< 0.001
* The full multivariable adjusting model included all baseline comorbidities and medications.								

Abbreviation: AA, aortic aneurysm; AD, aortic dissection; aHR, adjusted hazard ratio; CI, confidence interval; FQ, fluroquinolone; HR, hazard ratio; IR, incident rate (per 100,000 person-years)

The initial analysis showed a clear link between taking fluoroquinolones and a higher chance of developing AA/AD (HR 2.39, with a 95% CI of 2.18–2.62; the $p < .001$). Even after considering all the factors listed in Table 1, the use of fluoroquinolones was still significantly linked to an increased risk of getting AA/AD for the first time (the adjusted HR is 1.62, with a 95% CI of 1.47–1.78; $p < .001$).

Subgroup analysis

We further performed subgroup analysis to determine the effect of the baseline variables on AA/AD risk (Fig. 3). Almost all patients had increased HRs of entering AA/AD indicators in the favor of fluoroquinolones non-exposure, the risk for AA/AD was higher in patients younger than 40 years (HR 3.94, 95%CI 1.82–8.55). In addition, the risk for AA/AD was not different between the patients with and without fluoroquinolones exposure among those using intravenous steroids.

Critical factors to develop AA/AD in patients exposed to fluoroquinolones

Figure 4 shows how variables rank according to their average importance scores, as determined by LGR, RF, MARS, CART, and eXGBoost methods. The top ten most significant variables, listed from the most to the least important, are intravenous steroid, insulin, CCB, DM, oral steroid, beta-blockers, ACEI/ARB, hyperlipidemia, COPD, and patient's age (Supplementary Table S3 online).

Discussion

In this nationwide cohort study examining the impact of fluoroquinolones exposure on AA/AD incidence, our analyses revealed a 1.6-fold increased long-term risk of AA/AD among patients exposed to fluoroquinolones, with a significant association noted across nearly all subgroups that were analyzed. Using machine learning methods, we identified crucial factors contributing to AA/AD development in patients exposed to fluoroquinolones. The findings presented here are intended to assist healthcare professionals in creating systematic methods for the continuous observation and proactive prevention of AA/AD among individuals who have been treated with fluoroquinolone antibiotics to reduce the risk of potential health complications related to these antibiotics.

The mechanism underlying fluoroquinolones-induced AA/AD is not fully understood, although two hypotheses have been proposed. The first hypothesis posits that fluoroquinolones interfere with the integrity of the extracellular matrix, resulting in homeostatic dysregulation and impaired biomechanical strength in aorta, and ultimately triggering progressive aortic weakening, dissection, and rupture by upregulating the activity of matrix metalloproteinases (MMPs) and reducing the levels of tissue inhibitors of MMPs[25,26]. Increased MMP expression has been reported in smooth muscle cells in patients with abdominal AA[27] and in cornea and tendons in animals exposed to fluoroquinolones[14,28]. The second

hypothesis proposes that fluoroquinolones, which are DNA topoisomerase inhibitors, promote mitochondrial dysfunction, suppress cell proliferation, and induce apoptosis[29,30], ultimately leading to aortic damage.

In addition to fluoroquinolones, risk factors of AA/AD include older age, male sex, lifestyle habits such as cigarette smoking and stimulant abuse, and clinical conditions such as COPD, prolonged hypertension, obesity, atherosclerosis, chronic kidney disease, trauma, vasculitis, bacterial infection, and congenital connective tissue disorders [31–33]. Indeed, we also found that these previously reported factors were associated with AA/AD risk in Table 2. Further, we found that certain antihypertensive medications (ACEI/ARB, CCB, and beta-blockers) were associated with increased AA/AD risk. This finding contradicts previous studies linking the renin-angiotensin system to AA and suggesting that antihypertensive medications are beneficial for patient outcomes after the development of AA/AD[34,35]. One possible explanation for this discrepancy is that hypertension is a known risk factor for AA/AD[36] and that individuals with hypertension are often prescribed these antihypertensive medications. Therefore, in the present study, the association of antihypertensive medications with increased AA/AD risk might reflect the presence of high blood pressure, a known AA/AD risk factor, in these patients.

Based on our machine learning analysis, the top ten important factors for the development of AA/AD in patients with fluoroquinolones exposure were age, comorbidities such as DM, hyperlipidemia, and COPD, and medications including intravenous steroids, insulin, CCB, beta-blockers, and ACEI/ARB. Of these, intravenous steroid use was the top-scoring predictor of AA/AD. Of note, antihypertensive medication use might reflect preexisting high blood pressure. As indicated in Table 2, which outlines the risk determinants for AA/AD, and Fig. 4, which ranks the important risk factors, most of the top ten significant factors for AA/AD are also related to an increased risk of AA/AD. The only exceptions are diabetes mellitus (DM) and insulin use, which may play a role in reducing the risk of AA/AD in patients exposed to fluoroquinolones. Overall, the results mentioned above offer important insights for tracking patients exposed to fluoroquinolones.

Glucocorticoids are often used in combination with fluoroquinolones for inpatients. However, a case series reported that treatment with anabolic steroids increased the risk of AD in athletes, particularly in association with exercise [37]. Furthermore, Sendzik et al. reported that the combined use of steroids and fluoroquinolones increased the levels of MMPs and activated caspase 3, indicating apoptosis, in tenocyte cultures[38]. These results are consistent with the present study finding that steroid use, either intravenous or oral, might be associated with the development of AA/AD.

DM is a well-established risk factor for coronary and cerebrovascular diseases. However, the DM prevalence is surprisingly lower in individuals with abdominal AA than in those without abdominal AA (6–14% vs. 17–36%)[39]. In fact, a 3-year follow-up study found that DM was independently associated with reduced abdominal AA growth[40]. Similarly, Prakash et al. reported an inverse association between DM and the rate of hospitalization for thoracic AD[41]. In a meta-analysis including 14 studies and 15 794

patients, Li et al. found that the DM prevalence was lower in patients with AD than in those without AD (odds ratio 0.51, 95%CI 0.33–0.81)[42]. However, the mechanism underlying the beneficial effects of hyperglycemia in thoracic AD is not fully understood. In the present study, insulin had a beneficial effect and prevented the development of AA/AD. Insulin use may play an important role in the negative association observed between DM and the development of AA/AD.

Recent studies have increasingly shown the role of inflammation and macrophage infiltration in the development of AD[43,44]. In a murine model, Tomida et al. found that the use of indomethacin, an NSAID, prevented death due to abdominal AD and reduced the incidence of AD by up to 40%[45]. This effect might be attributed to the inhibition of monocyte transendothelial migration and blockade of the accumulation of monocytes/macrophages in the aortic wall. This is compatible with our findings, indicating the potential use of NSAIDs to prevent the development of AD.

The present study boasts several key strengths. Firstly, utilization of a nationwide database supports the generalizability of the study results. Secondly, the sample size and follow-up duration ensured a robust collection of AA/AD events. Thirdly, we employed machine learning methods were used to pinpoint important factors for the development of AA/AD in individuals exposed to fluoroquinolones. Lastly, the cohort study design minimized the risk of sampling bias, a common issue in case-control studies [46], that most previous research has used. Despite its strengths, the current study has a few potential weaknesses. Firstly, although the NHIRD database offered a large sample size, it did not include clinical information like imaging results, biochemical and microbiological data, blood pressure readings, and physical characteristics. Secondly, the study wasn't a randomized controlled trial, which meant that there were notable differences in the baseline characteristics of the two groups. However, to reduce these biases as much as possible, we used propensity score matching and multivariable adjustment. Finally, we were unable to confirm whether participants used fluoroquinolones before 2002 or after 2010 because of the limitations in our data availability and study design. Assuming the missing data was random in both groups, we could likely overlook the bias.

Conclusion

The long-term risk of AA/AD was 61% higher in patients with fluoroquinolones exposure than in those without fluoroquinolones exposure. Ten notable factors contributing to this correlation have been identified. We suggest that a sophisticated artificial intelligence system could be developed to predict the risk of developing AA/AD in patients treated with fluoroquinolone antibiotics based on our findings. Such powerful tool would enhance patient care by aiding healthcare professionals in making informed decisions regarding fluoroquinolone use.

Abbreviations

NHIRD
national health insurance research database

FQs
Fluoroquinolone.

Declarations

Author contributions

Conceived and designed the experiments: W-HW, F-YW, and C-Mingchih; performed the experiments: H-YC and T-MH; analyzed the data: H-YC, C-Mingchih, J-TN, and W-HW; contributed reagents/materials/analysis tools: all authors; wrote the manuscript: T-MH and W-HW; approved the manuscript: all authors.

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Data availability statement

The datasets used in this study are not available to the public because all claim records must be anonymized before they are released for analysis. The dataset is held by the Taiwan Ministry of Health and Welfare. (MOHW). Any researcher interested in accessing this dataset can apply for access. Please visit the website of the National Health Informatics Project of the MOHW (https://dep.mohw.gov.tw/DOS/mp-113.html.). If anyone would like to request the data from this study and is having difficulty accessing it, please contact the corresponding author, T-MH, for help.

References

1. Majalekar, P. P. & Shirote, P. J. Fluoroquinolones: Blessings Or Curses. *Curr Drug Targets* **21**, 1354-1370, doi:10.2174/1389450121666200621193355 (2020).
2. van der Linden, P. D., van de Lei, J., Nab, H. W., Knol, A. & Stricker, B. H. Achilles tendinitis associated with fluoroquinolones. *Br J Clin Pharmacol* **48**, 433-437, doi:10.1046/j.1365-2125.1999.00016.x (1999).
3. Kaleagasioglu, F. & Olcay, E. Fluoroquinolone-induced tendinopathy: etiology and preventive measures. *Tohoku J Exp Med* **226**, 251-258, doi:10.1620/tjem.226.251 (2012).
4. Kapoor, K. G., Hodge, D. O., St Sauver, J. L. & Barkmeier, A. J. Oral fluoroquinolones and the incidence of rhegmatogenous retinal detachment and symptomatic retinal breaks: a population-based study. *Ophthalmology* **121**, 1269-1273, doi:10.1016/j.ophtha.2013.12.006 (2014).
5. Wise, B. L., Peloquin, C., Choi, H., Lane, N. E. & Zhang, Y. Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. *Am J Med* **125**, 1228.e1223-1228.e1228, doi:10.1016/j.amjmed.2012.05.027 (2012).

6. Singh, S. & Nautiyal, A. Aortic Dissection and Aortic Aneurysms Associated with Fluoroquinolones: A Systematic Review and Meta-Analysis. *Am J Med* **130**, 1449-1457.e1449, doi:10.1016/j.amjmed.2017.06.029 (2017).
7. Lai, C. C., Wang, Y. H., Chen, K. H., Chen, C. H. & Wang, C. Y. The Association between the Risk of Aortic Aneurysm/Aortic Dissection and the Use of Fluroquinolones: A Systematic Review and Meta-Analysis. *Antibiotics (Basel)* **10**, doi:10.3390/antibiotics10060697 (2021).
8. Sampson, U. K. *et al.* Global and regional burden of aortic dissection and aneurysms: mortality trends in 21 world regions, 1990 to 2010. *Glob Heart* **9**, 171-180.e110, doi:10.1016/j.gheart.2013.12.010 (2014).
9. Powell, J. T. *et al.* Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. *Br J Surg* **104**, 166-178, doi:10.1002/bjs.10430 (2017).
10. Lee, C. C. *et al.* Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. *JAMA Intern Med* **175**, 1839-1847, doi:10.1001/jamainternmed.2015.5389 (2015).
11. Pasternak, B., Inghammar, M. & Svanström, H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *Bmj* **360**, k678, doi:10.1136/bmj.k678 (2018).
12. Gopalakrishnan, C. *et al.* Association of Fluoroquinolones With the Risk of Aortic Aneurysm or Aortic Dissection. *JAMA Intern Med* **180**, 1596-1605, doi:10.1001/jamainternmed.2020.4199 (2020).
13. Guzzardi, D. G. *et al.* Induction of human aortic myofibroblast-mediated extracellular matrix dysregulation: A potential mechanism of fluoroquinolone-associated aortopathy. *J Thorac Cardiovasc Surg* **157**, 109-119.e102, doi:10.1016/j.jtcvs.2018.08.079 (2019).
14. Tsai, W. C. *et al.* Ciprofloxacin up-regulates tendon cells to express matrix metalloproteinase-2 with degradation of type I collagen. *J Orthop Res* **29**, 67-73, doi:10.1002/jor.21196 (2011).
15. Jun, C. & Fang, B. Current progress of fluoroquinolones-increased risk of aortic aneurysm and dissection. *BMC Cardiovasc Disord* **21**, 470, doi:10.1186/s12872-021-02258-1 (2021).
16. Wee, I. *et al.* The association between fluoroquinolones and aortic dissection and aortic aneurysms: a systematic review and meta-analysis. *Sci Rep* **11**, 11073, doi:10.1038/s41598-021-90692-8 (2021).
17. Daneman, N., Lu, H. & Redelmeier, D. A. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open* **5**, e010077, doi:10.1136/bmjopen-2015-010077 (2015).
18. Maumus-Robert, S. *et al.* Short-Term Risk of Aortoiliac Aneurysm or Dissection Associated With Fluoroquinolone Use. *J Am Coll Cardiol* **73**, 875-877, doi:10.1016/j.jacc.2018.12.012 (2019).
19. Lee, C. C. *et al.* Oral Fluoroquinolone and the Risk of Aortic Dissection. *J Am Coll Cardiol* **72**, 1369-1378, doi:10.1016/j.jacc.2018.06.067 (2018).
20. Sommet, A. *et al.* What Fluoroquinolones Have the Highest Risk of Aortic Aneurysm? A Case/Non-case Study in VigiBase®. *J Gen Intern Med* **34**, 502-503, doi:10.1007/s11606-018-4774-2 (2019).

21. Hsieh, C. Y. *et al.* Taiwan's National Health Insurance Research Database: past and future. *Clin Epidemiol* **11**, 349-358, doi:10.2147/clep.S196293 (2019).
22. Tsai, M. H., Chen, M., Huang, Y. C., Liou, H. H. & Fang, Y. W. Corrigendum: The Protective Effects of Lipid-Lowering Agents on Cardiovascular Disease and Mortality in Maintenance Dialysis Patients: Propensity Score Analysis of a Population-Based Cohort Study. *Front Pharmacol* **13**, 894462, doi:10.3389/fphar.2022.894462 (2022).
23. Alsahaf, A., Petkov, N., Shenoy, V. & Azzopardi, G. A framework for feature selection through boosting. *Expert Systems with Applications* **187**, 115895 (2022).
24. Borboudakis, G. & Tsamardinos, I. Forward-backward selection with early dropping. *The Journal of Machine Learning Research* **20**, 276-314 (2019).
25. Hadi, T. *et al.* Macrophage-derived netrin-1 promotes abdominal aortic aneurysm formation by activating MMP3 in vascular smooth muscle cells. *Nat Commun* **9**, 5022, doi:10.1038/s41467-018-07495-1 (2018).
26. Sendzik, J., Shakibaei, M., Schäfer-Korting, M., Lode, H. & Stahlmann, R. Synergistic effects of dexamethasone and quinolones on human-derived tendon cells. *Int J Antimicrob Agents* **35**, 366-374, doi:10.1016/j.ijantimicag.2009.10.009 (2010).
27. Dilme, J. F. *et al.* Influence of cardiovascular risk factors on levels of matrix metalloproteinases 2 and 9 in human abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* **48**, 374-381, doi:10.1016/j.ejvs.2014.05.023 (2014).
28. Sharma, C. *et al.* Effect of fluoroquinolones on the expression of matrix metalloproteinase in debrided cornea of rats. *Toxicol Mech Methods* **21**, 6-12, doi:10.3109/15376516.2010.529183 (2011).
29. LeMaire, S. A. *et al.* Effect of Ciprofloxacin on Susceptibility to Aortic Dissection and Rupture in Mice. *JAMA Surg* **153**, e181804, doi:10.1001/jamasurg.2018.1804 (2018).
30. Tsai, W. C. *et al.* Ciprofloxacin-mediated inhibition of tenocyte migration and down-regulation of focal adhesion kinase phosphorylation. *Eur J Pharmacol* **607**, 23-26, doi:10.1016/j.ejphar.2009.02.006 (2009).
31. Kessler, V., Klopf, J., Eilenberg, W., Neumayer, C. & Brostjan, C. AAA Revisited: A Comprehensive Review of Risk Factors, Management, and Hallmarks of Pathogenesis. *Biomedicines* **10**, doi:10.3390/biomedicines10010094 (2022).
32. Wei, L. *et al.* Global Burden of Aortic Aneurysm and Attributable Risk Factors from 1990 to 2017. *Glob Heart* **16**, 35, doi:10.5334/gh.920 (2021).
33. Howard, D. P. *et al.* Population-based study of incidence of acute abdominal aortic aneurysms with projected impact of screening strategy. *Journal of the American Heart Association* **4**, e001926 (2015).
34. Fatini, C. *et al.* ACE DD genotype: a predisposing factor for abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* **29**, 227-232, doi:10.1016/j.ejvs.2004.12.018 (2005).

35. Nagashima, H. *et al.* Angiotensin II type 2 receptor mediates vascular smooth muscle cell apoptosis in cystic medial degeneration associated with Marfan's syndrome. *Circulation* **104**, I282-287, doi:10.1161/hc37t1.094856 (2001).
36. Hibino, M. *et al.* Blood Pressure, Hypertension, and the Risk of Aortic Dissection Incidence and Mortality: Results From the J-SCH Study, the UK Biobank Study, and a Meta-Analysis of Cohort Studies. *Circulation* **145**, 633-644, doi:10.1161/circulationaha.121.056546 (2022).
37. Heydari, A., Asadmobini, A. & Sabzi, F. Anabolic Steroid Use and Aortic Dissection in Athletes: A Case Series. *Oman Med J* **35**, e179, doi:10.5001/omj.2020.120 (2020).
38. Sendzik, J., Shakibaei, M., Schafer-Korting, M., Lode, H. & Stahlmann, R. Synergistic effects of dexamethasone and quinolones on human-derived tendon cells. *Int J Antimicrob Agents* **35**, 366-374, doi:10.1016/j.ijantimicag.2009.10.009 (2010).
39. Shantikumar, S., Ajjan, R., Porter, K. E. & Scott, D. J. Diabetes and the abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* **39**, 200-207, doi:10.1016/j.ejvs.2009.10.014 (2010).
40. Golledge, J. *et al.* Reduced expansion rate of abdominal aortic aneurysms in patients with diabetes may be related to aberrant monocyte-matrix interactions. *Eur Heart J* **29**, 665-672, doi:10.1093/eurheartj/ehm557 (2008).
41. Prakash, S. K., Pedroza, C., Khalil, Y. A. & Milewicz, D. M. Diabetes and reduced risk for thoracic aortic aneurysms and dissections: a nationwide case-control study. *J Am Heart Assoc* **1**, doi:10.1161/JAHA.111.000323 (2012).
42. Li, S. *et al.* Diabetes Mellitus Lowers the Risk of Aortic Dissection: a Systematic Review and Meta-Analysis. *Ann Vasc Surg* **74**, 209-219, doi:10.1016/j.avsg.2020.12.016 (2021).
43. Anzai, A. *et al.* Adventitial CXCL1/G-CSF expression in response to acute aortic dissection triggers local neutrophil recruitment and activation leading to aortic rupture. *Circ Res* **116**, 612-623, doi:10.1161/circresaha.116.304918 (2015).
44. Ju, X. *et al.* Interleukin-6-signal transducer and activator of transcription-3 signaling mediates aortic dissections induced by angiotensin II via the T-helper lymphocyte 17-interleukin 17 axis in C57BL/6 mice. *Arterioscler Thromb Vasc Biol* **33**, 1612-1621, doi:10.1161/atvbaha.112.301049 (2013).
45. Tomida, S. *et al.* Indomethacin reduces rates of aortic dissection and rupture of the abdominal aorta by inhibiting monocyte/macrophage accumulation in a murine model. *Sci Rep* **9**, 10751, doi:10.1038/s41598-019-46673-z (2019).
46. Mansournia, M. A., Jewell, N. P. & Greenland, S. Case-control matching: effects, misconceptions, and recommendations. *Eur J Epidemiol* **33**, 5-14, doi:10.1007/s10654-017-0325-0 (2018).

Figures

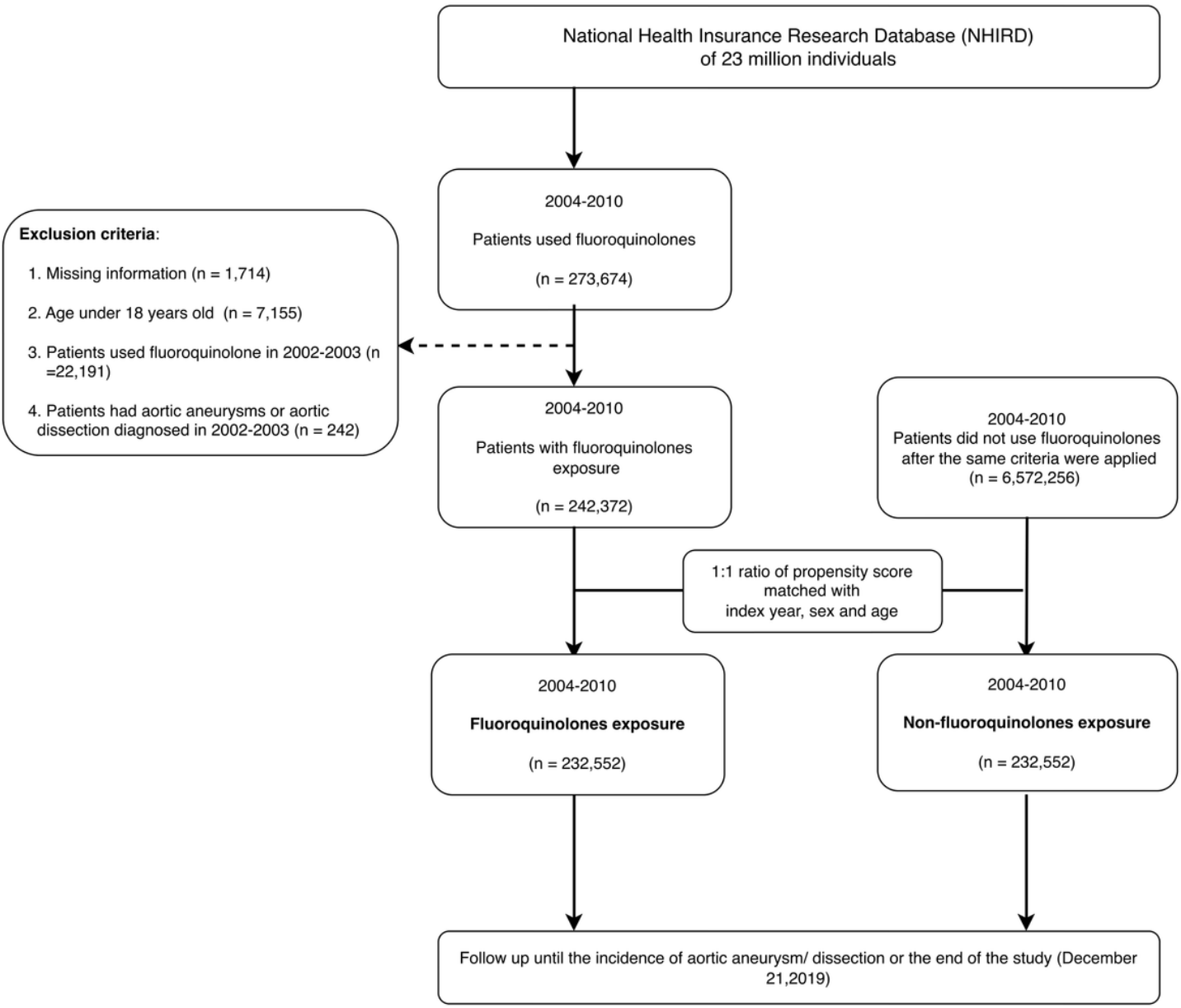

Figure 1

Schema of patient enrollment in the study.

Abbreviation: NHIRD, national health insurance research database; FQs, Fluoroquinolone.

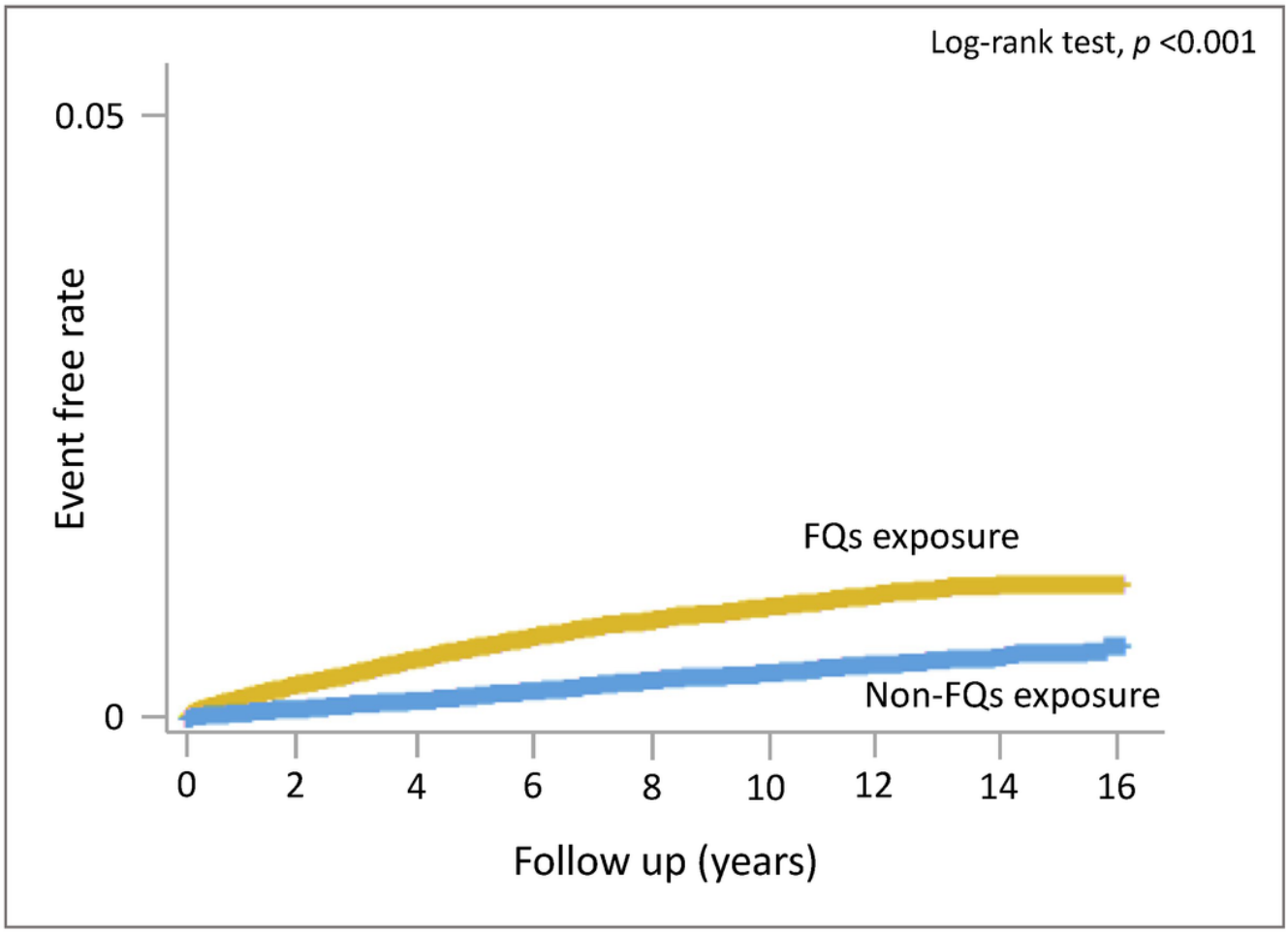

Figure 2

Kaplan-Meier curves on aortic aneurysm or aortic dissection associated with fluoroquinolone between groups exposed to fluoroquinolones and those not exposed.

Abbreviation: FQs, fluoroquinolone.

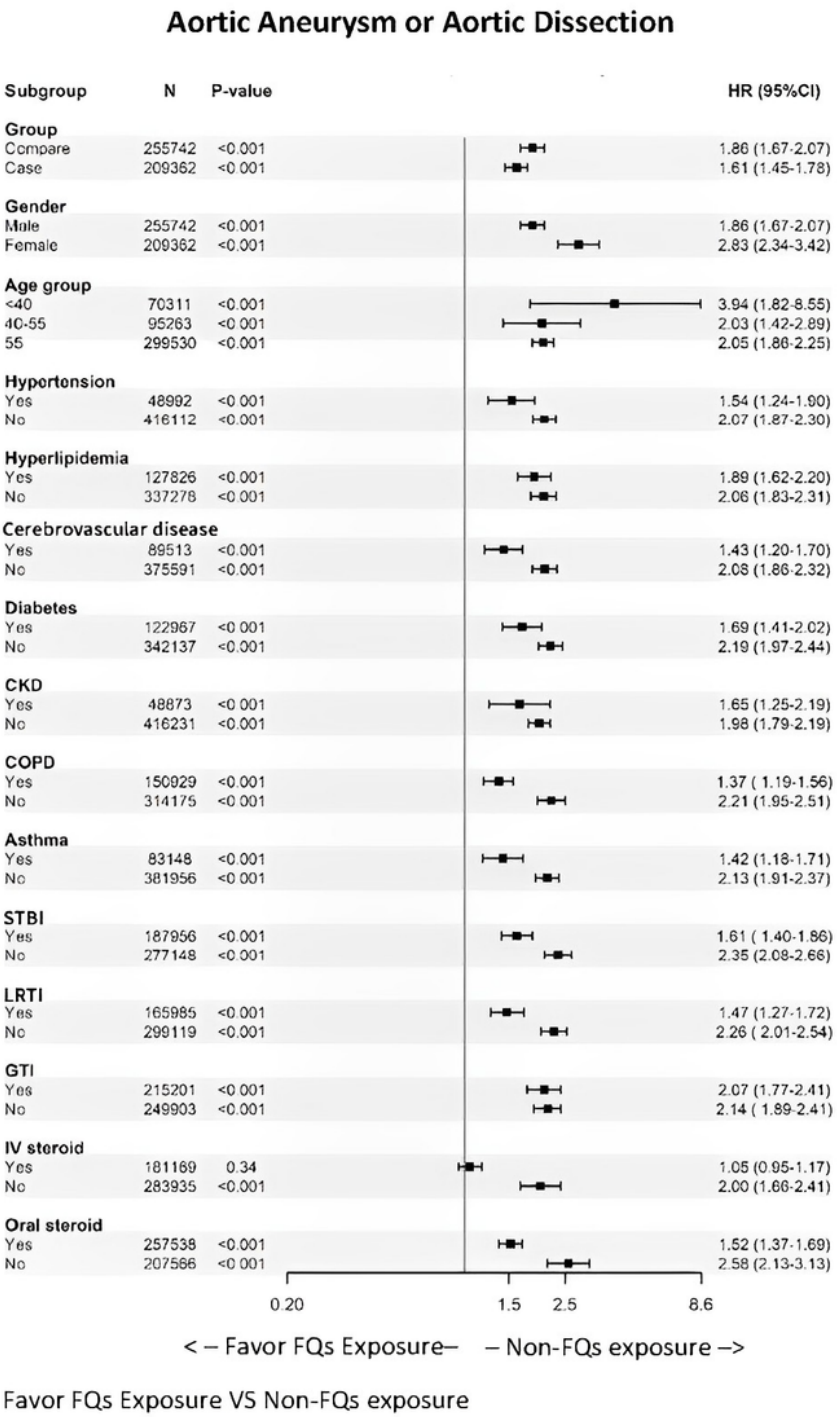

Figure 3

The subgroup analysis of the effect of fluoroquinolone exposure on the aortic aneurysm or aortic dissection

Abbreviation: FQs: Fluoroquinolone; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; STBI, soft tissue and bone infection; LRTI, lower respiratory tract infection; GTI, genital tract

infection.

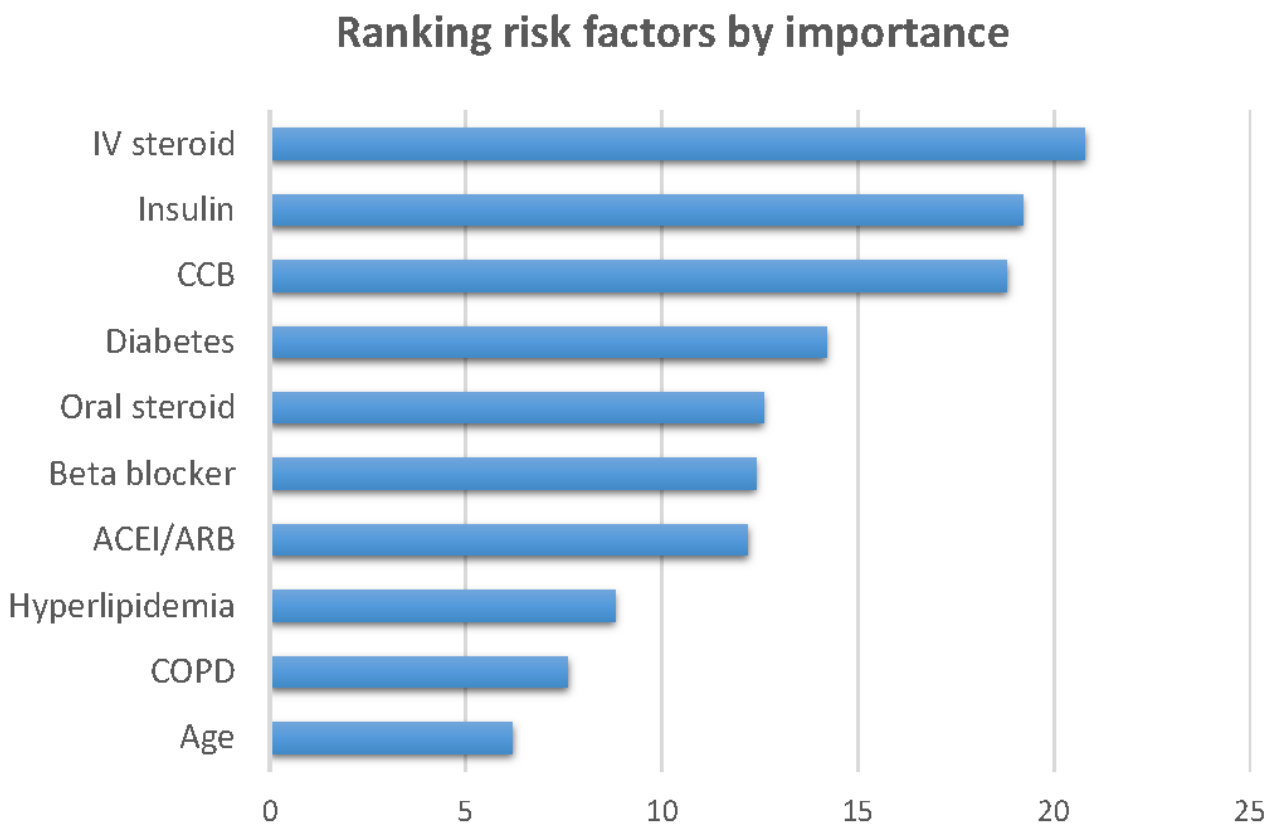

Figure 4

Ranking of parameters important factors for aortic dissection and aneurysm in patients with fluoroquinolones exposure based on machine learning methods

Abbreviation: IV, intravenous; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease.

Supplementary Files

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