Characteristics of organ cysts and their association with type A aortic dissection

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Abstract

Objective: We aimed to evaluate the incidence of organ cysts in patients with type A aortic dissection (TAAD) to assess the association between organ cysts and TAAD.

Methods: Between January 2018 and December 2018, all patients with TAAD undergoing aortic surgery at our center were enrolled into the study; patients undergoing isolated coronary artery bypass grafting at our center were selected as the control group. Baseline differences between the 2 groups were adjusted using propensity-score matching. The incidence of organ cysts was compared between the 2 groups in total and matched cohorts.

Results: We enrolled 290 patients with TAAD and 293 patients with coronary artery disease (control group). The incidence of all organ cysts, liver cysts, renal cysts, and other organ cysts, was significantly higher in the TAAD group than in the control group (50.0% vs. 35.5%, p<0.001; 24.5% vs. 10.2%, p<0.001; 33.4% vs. 24.9%, p=0.023; and 6.2% vs. 1.5%, p=0.005; respectively). Among the 191 propensity score–matched patient pairs, the incidence of organ cysts, liver cysts, renal cysts, and other organ cysts was also significantly higher in the TAAD group than in the control group (57.6% vs. 30.9%, p<0.001; 28.8% vs. 11.0%, p<0.001; 39.3% vs. 19.9%, p<0.001; and 8.4% vs. 1.0%, p=0.001; respectively). The incidence of cysts with single-organ and multiple-organ involvement was also significantly higher in the TAAD group than in the control group (34.0% vs. 20.4%, p=0.003; and 23.6% vs. 10.5%, p=0.001).

Conclusion: Our results show a higher incidence of organ cysts in patients with TAAD which is indicative of a common pathogenetic pathway between organ cysts and aortic dissection.

Keywords: organ cysts, pathogenesis, renal cysts, aortic dissection

Cite this article as: *Dun YJ, Guo HW, Chang Y, Wei K, Fan SY, Sun XG, et al. Characteristics of organ cysts and their association with type A aortic dissection. Anatol J Cardiol 2021; 25: 236-42.*

Introduction

Aortic dissection is the most frequently diagnosed lethal aortic disease (1). Clinically, type A aortic dissection (TAAD) is the most severe type of aortic dissection and has an overall high incidence and very high mortality. The pathogenesis of aortic dissection is complex and diverse (2). Several conditions, including hypertension, connective tissue disorders, cystic medial disease of aorta, atherosclerosis, that damage the aortic wall have been identified as risk factors of aortic dissection (2, 3). A meta-analysis also established a correlation between matrix metalloproteinase (MMP) polymorphisms and aortic dissection (4). This is indicative of the critical role MMP-triggered turnover of elastin and collagen likely plays in the pathogenesis of aortic dissection (4).

Organ cysts are a common structural organ disorder, and simple renal cysts (SRC) are one of the most common organ cysts, with a prevalence of 5%-41% in the general population (5, 6). The pathogenesis of SRC is also related to MMPs (7, 8). According to a study, renal cystic fluids contained MMPs, and MMP inhibitors could reduce cyst counts and renal weight (8, 9). In addition, MMP-related processes are involved in the development of cystic lung diseases (10), bone cysts (11), subchondral cysts (12), cystic ovarian cysts (13). We hypothesized

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Accepted Date: 09.10.2020 **Available Online Date:** 20.01.2021

DOI:10.14744/AnatolJCardiol.2020.99537

HIGHLIGHTS

- The incidence of organ cysts was higher in the type A aortic dissection (TAAD) group than in the control group.
- The incidence of organ cysts increased with age in both TAAD and control groups, and the incidence did not differ by sex in both groups.
- Organ cysts and aortic dissection may share a common pathogenesis, which remains to be elucidated.

that this finding extends to the involvement of MMPs in the pathogenesis of other organ cysts; we additionally hypothesized that organ cysts and aortic dissection share a common pathogenesis.

A few reports have revealed an association between SRC development and thoracic aortic aneurysm or aortic dissection (3, 14, 15). Per a report, the incidence of SRC in patients with TAAD is significantly higher than in those without (14), and when compared with matched controls, the patients with SRC were significantly more likely to have TAAD (3, 15). Per our clinical experience, the incidence of organ cysts other than SRC in patients with aortic dissection is also higher than that in the general population. However, the association between organ cysts and aortic dissection remained unestablished. Therefore, we aimed to determine whether development of aortic dissection and organ cysts is associated by comparing the incidence of organ cysts among patients with TAAD and those without thoracic aortic disease (control group).

Methods

Study population

Between January 2018 and December 2018, 861 patients received open aortic surgery and 802 patients received cardiac surgery in the Vascular Centre of Fuwai Hospital. All patients with TAAD during this period were enrolled as the study population. We selected patients with coronary artery disease (CAD) receiving isolated coronary artery bypass grafting at our center during this period as the control group. We selected these patients as controls given the lack of evidence supporting any inherent correlation with TAAD or organ cysts in such patients. We compared the incidence and characteristics of organ cysts between the TAAD and control groups. The study was approved by the Institutional Review Board of Fuwai Hospital. Need for obtaining informed consent was waived given this was a retrospective study.

Radioimaging evaluation

All patients in the study underwent aortic computed tomography (CT) scanning after admission. A variety of scanners were used to perform CT scanning, including Discovery CT 750 HD scanner (GE Healthcare, Massachusetts, USA), Revolution CT (GE Healthcare, Massachusetts, USA), Brilliance iCT (Philips, Amsterdam, Netherlands), and SOMATOM Definition or SOMATOM Definition Flash (Siemens Healthineers, Munich, Germany). The extent of the scan was from the level of the neck to the femoral head. The tube potential varied by the patient's body mass index (BMI): 120 kV when BMI >30 kg/m^2, 100 kV when BMI=20-30 kg/m^2, and 80 kV when BMI <20 kg/m^2. The x-ray tube current was also adjusted for each patient depending on the BMI. Contrast-enhanced acquisition was performed with an intravenous bolus injection of an iodinated contrast medium [iopromide (Ultravist) 370 mg I/mL, Bayer Healthcare, Berlin, Germany] at a volume of 1 mL/kg body weight with a saline chaser of 40 mL at a rate of 4-5 mL/s. CT images were reconstructed with a section thickness of 0.625 mm. The raw data of the scans were transferred to a workstation (Advantage Workstation Ver.4.6, GE Healthcare, Massachusetts, USA) for 3-dimensional image reconstruction (16).

Definition

Aortic dissection is the disruption of the medial layer that causes separation of the aortic walls and the formation of true and false lumens (17). The dissection involving the ascending aorta is classified as TAAD. CT imaging is used for the definitive diagnosis of TAAD. All patients with CAD were admitted to our center for surgery, where they underwent coronary angiography before admission. Based on the coronary angiography findings, all patients had met the criteria for coronary artery bypass grafting (18).

The occurrence of organ cysts was confirmed using CT imaging. The presence of an organ cyst was confirmed when an oval or round low-attenuation lesion with a thin wall and a size ≥4 mm was identified on the CT image without any obvious evidence of enhancement or separation (14, 15). All the cysts on the solid organs including the kidneys, liver, spleen, pancreas, ovaries, and the thyroid gland were included in the analysis. All imaging studies were examined, analyzed, and reported by 2 experienced radiologists.

Statistical analysis

Continuous variables were presented as means ± standard deviations and categorical variables as numbers (percentages). Normality was determined using the Kolmogorov-Smirnov test. The continuous variables distributed normally and non-normally were compared using the Student t test and the Mann Whitney U test, respectively. The Pearson chi-square test was used for between-group comparisons of categorical variables. Propensity-score matching was performed to adjust for the baseline differences between the 2 groups. The propensity score was estimated using 1:1 nearest available matching without replacement, based on an acceptable caliper width of 0.02 times the standard deviation of the logit of the propensity score. Age and sex were included in the propensity model. The matching

Anatol J Cardiol 2021; 25: 236-42
DOI:10.14744/AnatolJCardiol.2020.99537

was re-evaluated using standardized mean differences. SPSS software, version 24.0 (IBM Corp, NY, USA), was used for all statistical analyses. A p value of <0.05 was considered statistically significant.

Results

Total cohort

We enrolled 290 patients with TAAD and 293 patients with CAD (control group). The mean age of the TAAD and control groups, 52.7±12.1 years and 60.9±8.3 years, respectively, differed significantly (p<0.001). The proportion of men differed across the groups [TAAD: 200/290, (69%); control: 235/293 (80.2%); p=0.002]. The incidence of organ cysts was significantly higher in the TAAD group than in the control group [50.0% (145/290) vs. 35.5% (104/293), p<0.001).

We compared the incidence of organ cysts across the groups by the decade of age of the patients; incidence in the TAAD group was significantly higher in the 5th [52.3% (46/88) vs. 28.9% (26/90), p=0.001), 6th [68.7% (46/67) vs. 38.2% (50/131), p<0.001), and 7th decades of life and beyond [75.0% (18/24) vs. 48.8% (21/43), p=0.037]. Incidence increased in both the groups with increasing age (Fig. 1). The incidence of organ cysts in patients aged >50 years was significantly higher than that in patients aged <50 years in the TAAD group [61.5% (110/179) vs. 31.5% (35/111), p<0.001). Therefore, we performed a subgroup analysis by age. The incidence of organ cysts did not differ significantly among patients aged <50 years in both groups [TAAD: 31.5% (35/111), control: 24.1% (7/29), p=0.439]. However, among patients aged >50 years, the incidence of organ cysts was significantly higher in the TAAD group than in the control group [61.5% (110/179) vs. 36.7% (97/264), p<0.001; Fig. 2a]. Among patients aged >50 years, the incidence of liver cysts and SRC was also higher in the TAAD group than in the control group [liver cysts: 30.7% (55/179) vs. 10.2% (27/264), p<0.001; SRC: 43.0% (77/179) vs. 25.8% (68/179), p<0.001; Fig. 2b and 2c).

The incidence of organ cysts was evaluated separately for men and women in both the TAAD and control groups (Fig. 3). In the TAAD group, the incidence of organ cysts was 49.5% (99/200) and 51.1% (46/90) among men and women, respectively (p=0.8). In the control group, the incidence of organ cysts was 37.9% (89/235) for men and 25.9% (15/58) for women (p=0.087). In addition, no statistically significant differences in incidence of liver cysts or SRC were observed between men and women in both the TAAD and control groups.

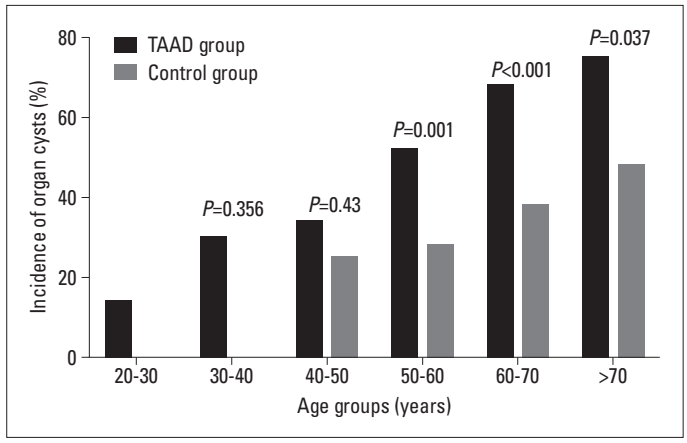

Figure 1. Incidence of organ cysts in patients with type A aortic dissection (TAAD) by age groups in comparison with the control group

The incidence of liver cysts, SRC, and other organ cysts was then evaluated separately for the entire cohort. Liver cysts, SRC, and other organ cysts all had significantly higher incidence in the TAAD group than in the control group [24.5% (71/290) vs. 10.2% (30/293), p<0.001; 33.4% (97/290) vs. 24.9% (73/293), p=0.023; and 6.2% (18/290) vs. 1.7% (5/293), p=0.005; respectively).

No significant difference was found in the incidence of single-organ cyst between the TAAD and control groups [21.7% (63/290) vs. 19.5% (57/293), p=0.498). However, the percentage of patients with multiple-organ cysts was much higher in the TAAD group than in the control group [28.3% (82/290) vs. 16.0% (47/293), p<0.001]. The incidence of both cysts with single-organ and multiple-organ involvement was also significantly higher in the TAAD group than in the control group [30.3% (88/290) vs. 20.9% (67/293), p=0.041; and 19.7% (57/290) vs. 12.6% (37/293), p=0.021, respectively]. The characteristics of organ cysts in the total cohort is shown in Table 1.

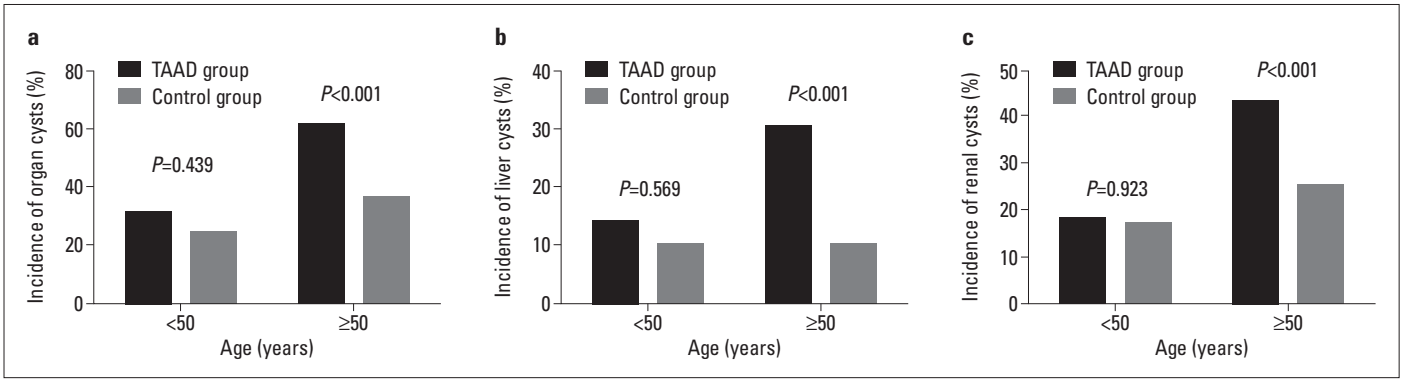

Figure 2. Incidence of organ cysts in patients with type A aortic dissection (TAAD) and the controls by age: (a) organ cysts, (b) liver cysts, (c) renal cysts

Table 1. Characteristics of organ cysts in the total cohort

Characteristic	Type A aortic dissection (n=290)	Coronary artery disease (n=293)	*P* value
Age (years)	52.7±12.1	60.9±8.3	<0.001
Sex, male	200 (69.0%)	235 (80.2%)	0.002
Concurrent organ cysts	145 (50.0%)	104 (35.5%)	<0.001
Liver cysts	71 (24.5%)	30 (10.2%)	<0.001
Single-liver cyst	37 (12.8%)	21 (7.2%)	0.024
Multiple-liver cysts	34 (11.7%)	9 (3.1%)	<0.001
Renal cysts	97 (33.4%)	73 (24.9%)	0.023
Single renal cyst	69 (23.8%)	58 (19.8%)	0.242
Single left renal cyst	36 (12.4%)	34 (11.6%)	0.764
Multiple left renal cysts	35 (12.1%)	26 (8.8%)	0.208
Single right renal cyst	33 (11.4%)	24 (8.2%)	0.195
Multiple right renal cysts	30 (10.3%)	24 (8.2%)	0.370
Other organ cysts	18 (6.2%)	5 (1.7%)	0.005
Single-organ cyst	63 (21.7%)	57 (19.5%)	0.498
Multiple-organ cysts	82 (28.3%)	47 (16.0%)	<0.001
Single-organ involvement	88 (30.3%)	67 (22.9%)	0.041
Single cyst on one organ	63 (21.7%)	57 (19.5%)	0.498
Multiple cysts on one organ	25 (8.6%)	10 (3.4%)	0.008
Two-organ involvement	39 (13.4%)	32 (10.9%)	0.351
Single/Single*	19 (6.6%)	9 (3.1%)	0.049
Single/Multiple**	1 (0.3%)	2 (0.7%)	0.569
Multiple/Multiple***	19 (6.6%)	21 (7.2%)	0.769
Three-organ involvement	16 (5.5%)	5 (1.7%)	0.014
Four-organ involvement	2 (0.7%)	0 (0)	0.154
Multiple-organ involvement (≥1)	57 (19.7%)	37 (12.6%)	0.021

*Both organs had a single cyst; **one organ had a single cyst, and the other organ had multiple cysts; ***both organs had multiple cysts

Propensity score–matched cohort

The analysis yielded 191 pairs of propensity score–matched observations. In the matched cohort, the mean age in the TAAD and control groups was 58.7±9.2 years and 58.0±8.1 years, respectively (p=0.429). The proportion of male patients was similar in both the TAAD and control groups (69.6% vs. 75.9%, p=0.168). The incidence of organ cysts in the matched cohort was recalculated. The incidence of organ cysts was 57.6% (110/191) in the TAAD group, which was significantly higher than that in the control group (30.9%, p<0.001).

Liver cysts, SRC, and other organ cysts all had higher incidence in the TAAD group than in the control group [28.8% (55/191) vs. 11.0% (21/191), p<0.001; 39.3% (75/191) vs. 19.9% (38/191), p<0.001; and 8.4% (16/191) vs. 1.0% (2/191), p=0.001]. No significant difference was found in the incidence of single-organ cyst between the 2 groups [TAAD: 23.0% (44/191), control: 17.3% (33/191); p=0.161]. However, the percentage of patients with multiple-organ cysts was much higher in the TAAD group than in the control group [34.6% (66/191) vs. 13.6% (26/191), p<0.001). Both cysts with single-organ and multi-organ involvement has significantly higher incidence in the TAAD group than in the control group [34.0% (65/191) vs. 20.4% (39/191), p=0.003; and 23.6% (45/191) vs. 10.5% (20/191), p=0.001). The character-

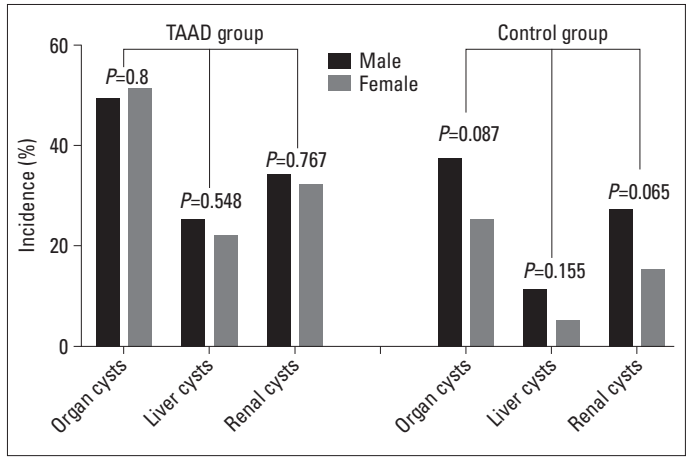

Figure 3. Incidence of organ cysts, liver cysts, and renal cysts in male and female patients with type A aortic dissection (TAAD) compared to that in the control group

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DOI:10.14744/AnatolJCardiol.2020.99537

Table 2. Characteristics of organ cysts in the propensity-score-matched cohort

Characteristic	Type A aortic dissection (n=191)	Coronary artery disease (n=191)	*P* value
Age (years)	58.7±9.2	58.0±8.1	0.429
Sex, male	133 (69.6%)	145 (75.9%)	0.168
Concurrent organ cysts	110 (57.6%)	59 (30.9%)	<0.001
Liver cysts	55 (28.8%)	21 (11.0%)	<0.001
Single-liver cyst	30 (15.7%)	15 (7.9%)	0.017
Multiple-liver cysts	25 (13.1%)	6 (3.1%)	<0.001
Renal cysts	75 (39.3%)	38 (19.9%)	<0.001
Single renal cyst	55 (28.8%)	33 (17.3%)	0.008
Single left renal cyst	24 (12.6%)	16 (8.4%)	0.181
Multiple left renal cysts	28 (14.7%)	11 (5.8%)	0.004
Single right renal cyst	29 (15.2%)	17 (8.9%)	0.059
Multiple right renal cysts	25 (13.1%)	11 (5.8%)	0.014
Other organ cysts	16 (8.4%)	2 (1.0%)	0.001
Single-organ cyst	44 (23.0%)	33 (17.3%)	0.161
Multiple-organ cysts	66 (34.6%)	26 (13.6%)	<0.001
Single-organ involvement	65 (34.0%)	39 (20.4%)	0.003
Single cyst on one organ	44 (23.0%)	33 (17.3%)	0.161
Multiple cysts on one organ	21 (11.0%)	6 (3.1%)	0.003
Two-organ involvement	29 (15.2%)	18 (9.4%)	0.087
Single/Single*	15 (7.9%)	6 (3.1%)	0.043
Single/Multiple**	0 (0)	2 (1.0%)	0.156
Multiple/Multiple***	14 (7.3%)	10 (5.2%)	0.399
Three-organ involvement	15 (7.9%)	2 (1.0%)	0.001
Four-organ involvement	1 (0.5%)	0 (0)	0.317
Multiple-organ involvement (≥1)	45 (23.6%)	20 (10.5%)	0.001

*Both organs had a single cyst; **one organ had a single cyst, and the other organ had multiple cysts; ***both organs had multiple cysts

istics of organ cysts in the propensity-score-matched cohort are summarized in Table 2.

Discussion

Results of this study reveal an increased incidence of organ cysts in patients with TAAD compared to that in patients with CAD. The higher incidence in the TAAD group sustained even after propensity score matching with adjustments for age and sex. Our results indicate an association between TAAD and organ cysts. Our findings support organ cysts as novel clinical markers of TAAD, similar to other known risk factors such as bicuspid aortic valve, intracranial aneurysm, bovine aortic arch, isolated left vertebral artery, and family history of aortic disease (14, 15).

Several studies have identified age as a risk factor for the development of organ cysts including SRC and liver cysts in the general population (5, 19-22). To control for age, we divided study patients and controls into different age groups (decades) and evaluated the incidence of organ cysts across each age group (Fig. 1). We found increasing incidence of organ cysts with increasing age in both the TAAD and control groups. Starting from the 5th age decade, overall incidence of organ cysts was significantly higher among patients with TAAD across all age decades. Further subgroup analysis in our study showed that differences in incidence of organ cysts, liver cysts, and SRC between the 2 groups only existed in patients aged >50 years. This result is consistent with that of a previous report (23). These findings suggest that age is an important contributing factor in the development of organ cysts. We posit that the association between organ cysts with aortic dissection is largely dependent on increasing age.

Our results showed no differences in incidence of organ cysts by sex in both the TAAD and control groups. Furthermore, incidence of liver cysts and SRC did not differ by sex. No previous study compared the incidence of organ cysts by sex in the general population. However, studies evaluating the incidence of SRC in the general population had reported the male-to-female ratio to range from 1.5 to 2.8 (14). However, our study results showed no male predominance of SRC, indicating differences

in pathogenesis of SRC between the patients with TAAD and the general population.

In our study, the incidence of organ cysts in the TAAD group and the control group was 50.0% and 35.5% (p<0.001), respectively. Furthermore, the incidence of liver cysts, SRC, and other organ cysts in the TAAD group was significantly higher than that in the control group. To adjust for age and sex, we performed a propensity score matching for the 2 groups and re-evaluated the incidence of organ cysts among the 2 groups again. After adjustment for age and sex, the incidence of organ cysts, liver cysts, SRC, and other organ cysts in the TAAD group remained significantly higher than that in the control group.

Given the lack of a large-scale epidemiological study evaluating the overall prevalence of organ cysts in the general population, we could not compare our results with those of the general population. Many studies have shown a higher incidence of SRC in the TAAD group than in the control group (14, 15, 23). The incidence of SRC in the general population was 5%-41% (5, 6) compared to 37.7%-47.1% (14, 15, 23) among patients with TAAD. In our study, the incidence of SRC in patients with TAAD was 33.4% (97/290), which is close to the aforementioned results. Some studies that evaluated the risk of aortic disease in patients with SRC found that these patients were significantly more likely to develop TAAD compared to those without SRC (3, 15). No previous study had analyzed the incidence of liver cysts in patients with TAAD. The incidence of liver cysts in patients with TAAD in our study was 24.5% (71/290), which is higher than that in the general population (2.5%-18%) (22, 24). In addition, the incidence of cysts with single-organ and multiple-organ involvement was also significantly higher in the TAAD group than in the control group. These findings indicate that the pathogenesis of organ cysts is related to that of aortic dissection.

The pathogenesis of aortic dissection is diverse and multifactorial. Connective tissue weakness or degenerative changes in the medial layer within the aortic wall were an important mechanism for aortic dissection. Any condition that weakens the integrity of the medial layer increases the risk of aortic dissection (23). MMPs are proteolytic enzymes that degrade the extracellular matrix (elastin, collagen, fibrillin) in the aorta (25). Imbalance between MMP activity and its tissue inhibitors could cause cystic medial degeneration and aortic wall weakening (14). Several studies have demonstrated that MMPs play an important role in the pathogenesis of aortic dissection (26-29).

The pathogenesis of organ cysts is not fully understood, whereas the pathogenesis of SRC is well studied. Many investigators have reported that MMPs are associated with the development of SRC (7, 8). High levels of MMP-2 and MMP-9 in the cystic fluid could be detected in both benign SRC and cystic renal cell carcinomas (8). MMP inhibitors significantly decrease the cyst counts and renal weight (9).

This indicates that MMPs are the common link between TAAD and SRC. MMP-related processes were also important in the formation of some other cystic diseases, including cystic lung diseases (10), bone cysts (11), subchondral cysts (12), cystic ovarian cysts (13). Only few studies on the pathogenesis of liver cysts, spleen cysts, pancreas cysts have been reported. Whether MMPs are involved in the development of these conditions was unknown. We hypothesized that if the development of organ cysts is associated with aortic dissection, MMPs could be the shared link between the 2 conditions.

The results of this study have an important clinical implication. The incidence of organ cysts is believed to be higher among patients with TAAD. The results support clinical suspicion of TAAD upon identification of organ cysts, particularly in patients with advanced age. Given the high incidence of organ cysts in the general population, we do not recommend CT screening for TAAD among patients with organ cysts. However, we believe some risk factors for aortic dissection, including hypertension and smoking, should be strictly controlled for these patients.

Study limitations

This study has some limitations. This was a retrospective, single-center study. We only enrolled patients with TAAD, but not patients with type B aortic dissection. The control group included patients with CAD, which might not be representative of the general population. Some baseline characteristics, including comorbidities and ethnicity, were not available in both groups. Furthermore, the definite number and maximum diameter of organ cysts were not obtained. Results of this study only suggest an association between organ cysts and TAAD and do not establish causation. This observational study does not clarify the molecular and pathophysiological mechanisms explaining the link between organ cysts and TAAD. We hope that the underlying molecular and pathophysiological mechanisms are elucidated in future studies.

Conclusion

The incidence of organ cysts was higher among patients with TAAD than among patients with CAD. The incidence of organ cysts increased with age in both TAAD and control groups, and the incidence did not differ by sex in both groups. Organ cysts and aortic dissection may share a common pathogenesis. However, this clinical observation needs further studies elucidating the definite molecular and pathophysiological mechanisms to establish the link between the pathogenesis of organ cysts and aortic dissection.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – Y.J.D., H.W.G.; Design – Y.J.D., H.W.G.; Supervision – H.W.G., X.G.S., X.Y.Q., C.T.Y.; Fundings – H.W.G.; Materials – K.W., S.Y.F.; Data collection and/or processing – Y.J.D., Y.C., K.W.; Analysis and/or interpretation – Y.J.D., H.W.G.; Literature search – H.W.G.; Writing – Y.J.D., H.W.G.; Critical review – Y.J.D., H.W.G.

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DOI:10.14744/AnatolJCardiol.2020.99537

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