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Clinical Investigation

Cardiovascular Disease and Inpatient Complications in Turner Syndrome: A Propensity Score Analysis

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Abstract

Background: Turner syndrome is a genetic disorder that occurs in female individuals and is characterized by the absence of 1 of the X chromosomes. This study examined the risk of cardiovascular disease and inpatient clinical outcomes in patients with Turner syndrome.

Methods: Data were extracted from the Nationwide Inpatient Sample 2016 database. Propensity score analysis was used to match women with Turner syndrome and women without Turner syndrome admitted to a hospital in the same year to evaluate the risk of cardiovascular disease and inpatient clinical outcomes in patients with Turner syndrome.

Results: After 1:1 matching, 710 women with Turner syndrome and 710 women without Turner syndrome were included in the final analysis. Compared with women without Turner syndrome, women with Turner syndrome were more likely to have a bicuspid aortic valve (9.4% vs 0.01%; $P < .01$), coarctation of the aorta (5.8% vs 0.3%; $P < .01$), atrial septal defect (6.1% vs 0.8%; $P < .01$), and patent ductus arteriosus (4.6% vs 0.6%; $P < .01$). Patients with Turner syndrome were more likely to have an aortic aneurysm (odds ratio [OR], 2.46 [95% CI, 1.02-5.98]; $P = .046$), ischemic heart disease (OR, 1.66 [95% CI, 1.10-2.5]; $P = .02$), heart failure (OR, 3.15 [95% CI, 1.99-4.99]; $P < .01$), and atrial fibrillation or flutter (OR, 2.48 [95% CI, 1.42-4.34]; $P < .01$). Patients with Turner syndrome were more likely to have pulmonary arterial hypertension (OR, 2.12 [95% CI, 1.08-4.14]; $P = .03$) and acute kidney injury (OR, 1.60 [95% CI, 1.06-2.42]; $P = .03$) and to require mechanical ventilation (OR, 1.66 [95% CI, 1.04-2.68]; $P = .04$).

Conclusion: Turner syndrome is associated with an increased rate of cardiovascular disease and inpatient complications. These findings suggest that patients with Turner syndrome should be screened and monitored closely for cardiovascular disease and inpatient complications.

Keywords: Turner syndrome; risk factors; heart defects, congenital; cardiovascular diseases

Introduction

Turner syndrome is a chromosomal disorder affecting 1 in 2,500 female live births.[1] It is caused by the absence of 1 of the X chromosomes, resulting in only 1 X chromosome in some or all of the body cells.[2] Turner syndrome was first described by Otto Ullrich[3] in 1930 based on the clinical features of this syndrome, and it is considered one of the most common chromosomal disorders affecting female individuals.[4] This syndrome is diagnosed by the presence of clinical features and confirmed by cytogenetic testing.[5] Turner syndrome is characterized by a variety of physical and developmental abnormalities, including short stature, lymphatic abnormalities, skeletal abnormalities, delayed puberty, and infertility as a result of ovarian insufficiency.[6]

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Cardiovascular disease (CVD) is a substantial health concern in patients with Turner syndrome and the most common cause of morbidity and mortality in this patient population.[7] Several studies have shown that bicuspid aortic valve and aortic coarctation are the most common congenital heart disease in patients with Turner syndrome, leading to aortic dilatation and aortic dissection.[8-11] Other studies have shown that Turner syndrome also increases the risk of atherosclerotic CVD and its risk factors, such as diabetes, hyperlipidemia, and hypertension[12-15]; however, the risks of acquired CVD and inpatient clinical outcomes in these patients have not been studied extensively. Knowing these risks would improve early detection and screening for these diseases among patients with Turner syndrome.

This study aimed to examine the risk of acquired CVD and inpatient clinical outcomes in patients with Turner syndrome compared with patients without Turner syndrome.

Key Points

- This study identified a higher prevalence of previously unreported congenital heart anomalies in patients with Turner syndrome.
- Turner syndrome is associated with an increase in traditional cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia.
- Patients with Turner syndrome are more likely to have acquired CVDs, such as ischemic heart disease, heart failure, and aortic aneurysms.
- Turner syndrome is associated with a higher risk of inpatient complications such as acute kidney injury and the need for mechanical ventilation.
- Early screening and close monitoring for CVD are crucial for the long-term health outcomes of patients with Turner syndrome.

Abbreviations and Acronyms

CVD	cardiovascular disease
ICD-10	*International Statistical Classification of Diseases, Tenth Revision*
NIS	Nationwide Inpatient Sample
OR	odds ratio

Patients and Methods

The Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project was used in this study. The NIS is a large, nationally representative sample of patient hospital discharge data in the United States. It was designed to evaluate inpatient health care costs, access, utilization, quality, and outcomes. The NIS contains patients' baseline demographic characteristics, diagnoses, procedures, and outcomes.[16,17] All female patients admitted with Turner syndrome in 2016 were identified using the *International Statistical Classification of Diseases, Tenth Revision (ICD-10)* code for Turner syndrome: Q96. Patients with Turner syndrome were compared with all female patients without Turner syndrome admitted in the same year.

Clinical Variables and Outcomes

The following baseline demographic characteristics were collected: age, race, and hospital region. The following health characteristics were collected: congenital heart disease, cardiovascular risk factors, acquired CVD, and inpatient clinical outcomes. Congenital heart disease was identified using *ICD-10* codes for bicuspid aortic valve (Q23.1), atrial septal defect (Q21.1), coarctation of the aorta (Q25.1), patent ductus arteriosus (Q25.0), and other congenital heart defects. Cardiovascular risk factors were identified using *ICD-10* codes for hypertension (I10), hyperlipidemia (E78.0), type 2 diabetes (E11), and smoking (F17). Acquired CVD was identified using *ICD-10* codes for aortic aneurysm (I71), aortic dissection (I71.0), ischemic heart diseases (I20-I25), heart failure (I50), pulmonary hypertension (I27.0), atrial fibrillation/flutter (I48), and cerebrovascular accidents (I63). Inpatient clinical outcomes were identified using *ICD-10* codes for acute kidney injury (N17), cardiogenic shock (R57.0), and the need for mechanical ventilation and support (5A19, 5A09).

Statistical Analysis

To account for potential confounding by baseline characteristics, propensity score matching was employed to estimate the effect of having Turner syndrome on female patients. A multivariable logistic regression model was developed to predict the probability (propensity score) of having Turner syndrome at admission for each female patient. The model incorporated predefined baseline characteristics, including age, race (White), hospital region, smoking status, and comorbidities (diabetes, hypertension, and hyperlipidemia). Based on the propensity score, 1:1 nearest-neighbor matching without replacement was used. This approach aimed to create matched cohorts with similar propensity scores between women with Turner syndrome and women without Turner syndrome.[18,19]

The effectiveness of matching in balancing these characteristics was assessed by comparing the distribution of propensity scores before and after

matching. Standardized mean differences were also calculated to quantify covariate balance. Figure 1 shows that the propensity score distribution differed in the unmatched groups but was similar in the matched groups. Figure 2 depicts a reduction in the standardized mean differences in the matched groups compared with the unmatched groups. The standardized mean differences in the matched sample were less than 2%.

The baseline demographic and clinical characteristics were reported as percentages for categorical variables and medians for continuous variables. The prevalence of congenital heart disease was compared between the matched groups to determine the significant differences between women with and without Turner syndrome. The χ^2 and Wilcoxon rank sum tests were used to compare the 2 groups' baseline categorical

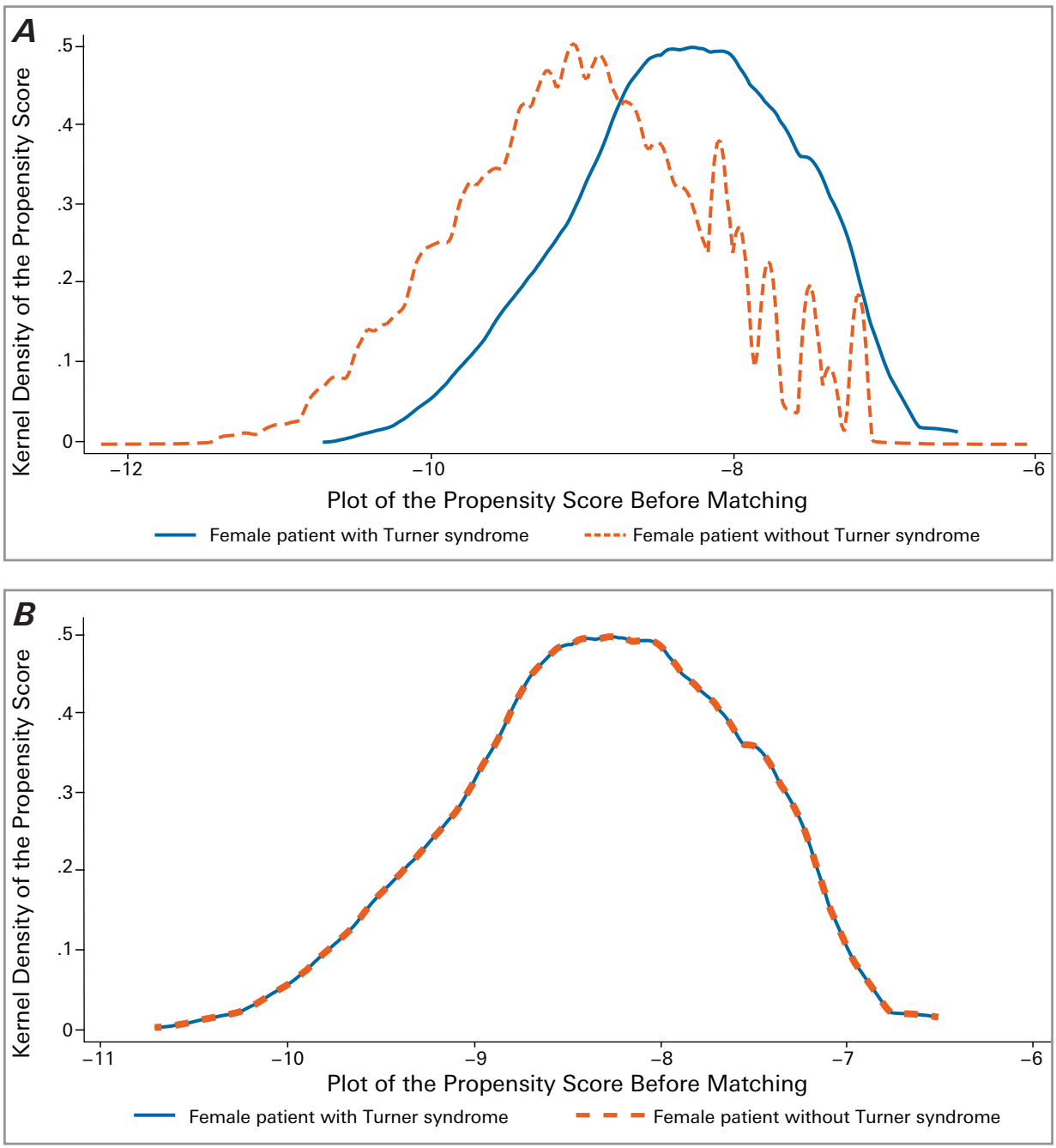

Fig. 1 Line graphs show that the propensity score distribution (**A**) differs between the 2 groups in the unmatched analysis but (**B**) is similar in the matched analysis.

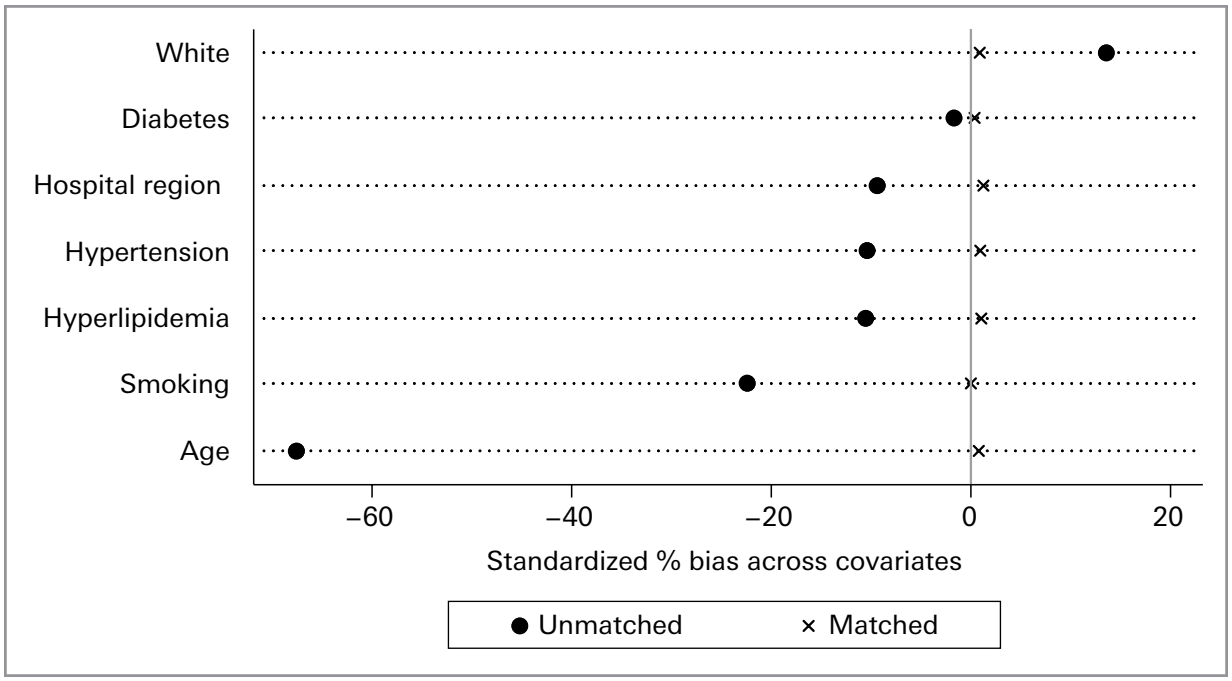

Fig. 2 The forest plot depicts a reduction in the standardized differences in the matched groups compared with those in the unmatched groups. The standardized differences in the matched sample were less than 2%.

and continuous variables. Logistic regression models were used to calculate the odds ratios (ORs) of acquired CVD and inpatient mortality after matching. $P < .05$ was considered statistically significant. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc) and STATA, version 16.1 (StataCorp LLC) software.

Results

Unmatched Analysis

Baseline Demographic Characteristics and Cardiovascular Risk Factors

Before matching, a significant imbalance existed between the Turner syndrome group (n = 711) and the control group (n = 4,048,309) (Table I). Patients with Turner syndrome were younger (median [IQR] age, 33 [10-49] years vs 51 [27-71] years; $P < .01$) and more likely to be White (68% vs 61%; $P < .01$). After adjusting for age, patients with Turner syndrome had a higher likelihood of having traditional cardiovascular risk factors, including diabetes (OR, 2.02 [95% CI, 1.65-2.48]; $P < .01$), hypertension (OR, 2.05 [95% CI, 1.70-2.47]; $P < .01$), and hyperlipidemia (OR, 2.19 [95% CI, 1.78-2.70]; $P < .01$) but were less likely to smoke (OR, 0.45 [95% CI, 0.32-0.63]; $P < .01$).

Matched Analysis

Baseline Demographic Characteristics and Congenital Heart Disease

Propensity score matching successfully addressed the imbalances between women with and without Turner syndrome. After matching (n = 710 for both the Turner syndrome and control groups), there were no significant differences in baseline characteristics, with all standardized mean differences below 2% (Table II).

Patients with Turner syndrome had a significantly higher prevalence of congenital cardiac defects and had longer hospital lengths of stay (median [IQR], 4 [2-7] days vs 3 [2-5] days; $P < .01$). The most common congenital cardiac defects in the Turner syndrome group were bicuspid aortic valve (9.4%), atrial septal defect (6.1%), coarctation of the aorta (5.8%), and patent ductus arteriosus (4.6%). Patients with Turner syndrome had a significantly higher prevalence of hypoplastic left heart syndrome (1.5%), ventricular septal defect (1.4%), and pulmonary vein return abnormalities (1.4%) compared with patients without Turner syndrome.

TABLE I. Baseline Demographic and Clinical Characteristics for Patients With and Without Turner Syndrome

	Before matching			After matching			
	Patients without Turner syndrome	Patients with Turner syndrome	*P* value	Patients without Turner syndrome	Patients with Turner syndrome	*P* value	Standardized mean difference, %
No.							
Demographic characteristics							
Age, median (IQR), y	51 (27-71)	32.5 (10.0-49.0)	<.01	32 (10-49)	32.5 (10.0-49.0)	.87	0.8
White race, No. (%)	2,470,785 (61.0)	480 (67.5)	<.01	476 (67.0)	479 (67.5)	.87	0.9
Hospital region, No. (%)			<.01			.99	1.3
Northeast	736,291 (18.2)	144 (20.3)		146 (20.6)	143 (20.1)		
Midwest	899,865 (22.2)	190 (26.7)		190 (26.8)	190 (26.8)		
South	1,603,846 (39.6)	241 (33.9)		241 (33.9)	241 (33.9)		
West	808,307 (20.0)	136 (19.1)		133 (18.7)	136 (19.2)		
Health characteristics, No. (%)							
Smoking	434,688 (10.7)	34 (4.8)	<.01	34 (4.8)	34 (4.8)	.99	0.0
Diabetes	738,001 (18.2)	125 (17.6)	.65	124 (17.5)	125 (17.6)	.94	0.4
Hypertension	1,230,524 (30.4)	183 (25.7)	.01	180 (25.4)	183 (25.8)	.86	0.9
Hyperlipidemia	936,318 (23.1)	134 (18.8)	.01	131 (18.5)	134 (18.9)	.84	1.0

P < .05 was considered statistically significant.

Acquired CVD and Inpatient Clinical Outcomes

Following 1:1 matching (Table III), patients with Turner syndrome had a significantly increased risk of various cardiovascular complications compared with patients in the control group. These complications included aortic aneurysm (OR, 2.46 [95% CI, 1.02-5.98]; *P* = .046), ischemic heart disease (OR, 1.66 [95% CI, 1.10-2.50]; *P* = .02), and heart failure (OR, 3.15 [95% CI, 1.99-4.99]; *P* < .01). They were more likely to experience atrial fibrillation or flutter (OR, 2.48 [95% CI, 1.42-4.34]; *P* < .01), pulmonary arterial hypertension (OR, 2.12 [95% CI, 1.08-4.14]; *P* = .03), and acute kidney injury (OR, 1.60 [95% CI, 1.06-2.42]; *P* = .03). They also required mechanical ventilation more often (OR, 1.66 [95% CI, 1.04-2.68]; *P* = .04). Inpatient death was higher in patients with Turner syndrome but did not reach statistical significance after 1:1 matching.

Discussion

This study revealed that Turner syndrome is associated with the increased prevalence of several congenital anomalies, some of which have not been reported in medical literature. This study supports the findings of previous studies, however, which showed that patients with Turner syndrome are at high risk of CVD risk factors. This study also revealed that Turner syndrome is associated with a higher risk of acquired CVD and inpatient complications.

Turner syndrome increases the risk of congenital heart disease. Mazzanti et al[20] showed that the most common congenital heart diseases in patients with Turner syndrome were bicuspid aortic valve, coarctation of the aorta, and aortic valve disease; however, other congenital heart anomalies have not been studied extensively in patients with Turner syndrome.[20-23] The current study showed that the most common prevalent congenital heart diseases in patients with Turner syndrome are bicuspid aortic valve, atrial septal defect, coarctation of the aorta, patent ductus arteriosus, hypoplastic left heart syndrome, ventricular septal defect, and pulmonary vein return abnormalities. Patients with Turner syndrome have several other congenital heart diseases, such as pulmonary artery stenosis, pulmonary valve stenosis, atresia of the aortic artery, atresia of the pulmonary artery, supra-aortic stenosis, pulmonary infundibular stenosis, persistent left superior vena cava, congenital tricuspid stenosis, double outlet right ventricle, atrioventricular septal defect, tetralogy of Fallot, and hypoplastic right heart syndrome; however, these congenital anomalies did not reach statistical significance after 1:1 matching.

TABLE II. Baseline Demographic and Clinical Characteristics for Patients With and Without Turner Syndrome After Propensity Matching

	After matching		
	Patients without Turner syndrome	**Patients with Turner syndrome**	***P* value**
No.	710	710	
Congenital cardiac malformations, No. (%)			
Bicuspid aortic valve	1 (0.1)	67 (9.4)	<.01
Atrial septal defect	6 (0.8)	43 (6.1)	<.01
Coarctation of aorta	2 (0.3)	41 (5.8)	<.01
Patent ductus arteriosus	4 (0.6)	33 (4.6)	<.01
Hypoplastic left heart syndrome	1 (0.1)	11 (1.5)	<.01
Ventricular septal defect	2 (0.3)	10 (1.4)	.02
Pulmonary venous return abnormalities	0 (0.0)	10 (1.4)	<.01
Pulmonary artery stenosis	1 (0.1)	3 (0.4)	.32
Pulmonary valve stenosis	0 (0.0)	2 (0.3)	.16
Atresia of aortic artery	0 (0.0)	2 (0.3)	.16
Atresia of pulmonary artery	0 (0.0)	1 (0.1)	.32
Supra-aortic stenosis	0 (0.0)	1 (0.1)	.32
Pulmonary infundibular stenosis	0 (0.0)	1 (0.1)	.32
Persistent left superior vena cava	0 (0.0)	1 (0.1)	.32
Congenital tricuspid stenosis	0 (0.0)	1 (0.1)	.32
Double outlet right ventricle	1 (0.1)	1 (0.1)	.99
Atrioventricular septal defect	0 (0.0)	1 (0.1)	.32
Tetralogy of Fallot	1 (0.1)	1 (0.1)	.99
Hypoplastic right heart syndrome	0 (0.0)	1 (0.1)	.32
Length of hospital stay, median (IQR), d	3 (2-5)	4 (2-7)	<.01

P < .05 was considered statistically significant.

In the current study, CVD risk factors, including hypertension, hyperlipidemia, and diabetes, were higher among patients with Turner syndrome after adjusting for age. The results of this study were partially similar to the results of Landin-Wilhelmsen et al,[24] which showed that patients with Turner syndrome were at higher risk of hypertension and less likely to be smokers, with no increase in the risk of hyperlipidemia or diabetes. Landin-Wilhelmsen and colleagues' study was unable to detect the differences in the risk of diabetes and hyperlipidemia between women with and women without Turner syndrome because it included 100 women with Turner syndrome. Hyperlipidemia is expected to be high in patients with Turner syndrome because of their lack of female sex hormones, but patients with Turner syndrome who received female sex hormone therapy had a reduction in their lipid profile.[25,26] The risk of diabetes was higher in patients with Turner syndrome because patients with Turner syndrome have insulin deficiency and are insulin resistant.[15,17,27,28]

TABLE III. Odds Ratio of Cardiovascular Disease and In-Hospital Complications Among Patients With Turner Syndrome Compared With Patients Without Turner Syndrome After Propensity Matching

	Odds ratio	95% CI	*P* value
Aortic aneurysm	2.46	1.02-5.98	.046
Aortic dissection	2.00	0.18-22.14	.57
Ischemic heart disease	1.66	1.10-2.50	.02
Heart failure	3.15	1.99-4.99	<.01
Pulmonary arterial hypertension	2.12	1.08-4.14	.03
Atrial fibrillation/flutter	2.48	1.42-4.34	<.01
Cerebrovascular accident	2.02	0.75-5.40	.16
Acute kidney injury	1.60	1.06-2.42	.03
Mechanical ventilation	1.66	1.04-2.68	.04
Inpatient death	1.11	0.45-2.75	.82

P < .05 was considered statistically significant.

Patients with Turner syndrome are at higher risk of acquired CVD and, in the current study, were shown to have a higher risk of ischemic heart disease, atrial fibrillation, and aortic aneurysm, findings consistent with previous studies.[14,23,29,30] The current study is the first to show that Turner syndrome is associated with a higher risk of heart failure and pulmonary arterial hypertension, which is expected as a result of ischemic heart disease and congenital cardiac anomalies. Patients with Turner syndrome had a higher risk of acute kidney injury and required more mechanical ventilation during hospital admissions. Screening these patients for CVD early in life and monitoring them closely for any signs or symptoms of CVD should therefore be considered.

Overall, this study found that Turner syndrome is associated with a higher prevalence of CVD and inpatient complications. By exploring the risks of acquired CVD and inpatient complications, the study aimed to raise awareness of these risks so that physicians can identify these diseases and complications earlier. Early detection and treatment of CVD risk factors, CVD, and inpatient complications in patients with Turner syndrome is essential to improving the long-term health outcomes and well-being of this patient population.

Limitations

This study was limited by its retrospective design and the use of administrative data. The retrospective nature of this study permits identifying only associations rather than causal relationships. As with any study, there is always the possibility of unknown confounding from variables not included in the analysis because they are unavailable in NIS, such as a family history of premature CVD and the patient's physical activities, laboratory test results, and medications.

Conclusion

This study found a strong association between Turner syndrome and an increased prevalence of both congenital heart defects and a broader spectrum of acquired CVDs and inpatient complications. These findings highlight the importance of early screening and close monitoring for CVD in patients with Turner syndrome. Early detection of and intervention for CVD risk factors and complications are crucial for improving long-term health outcomes in this population. Further research is needed to explore preventive measures and interventions tailored to reduce the risk of CVD in patients with Turner syndrome.

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