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Bicuspid Aortic Valve Disease in Turner Syndrome: A Meta-Analysis of Prevalence

Erick Thokerunga[1], Yahya-Abdullahi Ali[2], Christopher Ntege[3*]

[1]Department of Clinical Laboratory Medicine, Center for Gene Diagnosis, Zhongnan Hospital of University, Wuhan, China
[2]Department of Cardiology, First Affiliated Renmin Hospital of Wuhan University, Wuhan, China
[3]Department of Radiology and Nuclear Medicine, Zhongnan Hospital of Wuhan University, Wuhan, China
Email: *ntegechris@whu.edu.cn

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Abstract

Turner syndrome patients partially or completely lack the X chromosome. 1 - 2500 female live births are affected. Clinical features include webbed neck, short stature, broad chest etc. Bicuspid aortic valve disease (BAV) occurs in more than 30% of Turner syndrome patients causing significant morbidity and mortality. We aimed to establish a more reliable estimate of the prevalence of BAV in Turner syndrome. PubMed, Embase and PsycINFO databases were searched until 2022. Review Manager (RevMan 5.4.1) and the JASP software (0.16.00) were used for meta-analysis. 15 studies with a total of 3189 patients were combined. The pooled prevalence of BAV in Turner syndrome was 22.0% (95% CI: 15.0% - 29.0%). Sub group analysis by 45, X0 karyotype and age had prevalence of 24.0% and 8% respectively. The studies had high heterogeneity and possible publication biases. In summary, the study established that the prevalence of BAV in Turner syndrome patients diagnosed by echocardiogram, CT and MRI scans, is 22.0%, and 24% in patients with true monosomy 45, X0 karyotypes. Routine BAV exam should pay particular attention to monosomy 45, X0 karyotype patients, and where possible, CT and MRI should always accompany echocardiography for BAV screening, especially for pediatrics.

Keywords

Bicuspid Aortic Valve, Turner Syndrome, Meta-Analysis, Prevalence

1. Introduction

Turner syndrome is a genetic anomaly in which an individual partially or completely lacks the X chromosome [1]. It occurs in about 1 - 2500 female live births [2], and physically presents with clinical features such as a webbed neck, short

stature, cubitus valgus, a broad chest, gonadal dysgenesis, and late puberty [3]. Close to 50% of Turner syndrome patients develop congenitally or acquired cardiovascular complications causing significant morbidity and mortality [4], among them are aortic coarctation, elongated transverse aorta, partial anomalous pulmonary venous return, and bicuspid aortic valves [5].

Bicuspid aortic valve disease (BAV) is a congenital heart defect in which the aorta has only two instead of the usual three valve leaflets [6]. BAV is a clinical feature of more than 30% of Turner syndrome patients [7]. It's often asymptomatic in the general population and only discovered on routine medical check-ups [8]. However, in Turner syndrome, the co-occurrence of other heart defects such as aortic coarctation exacerbates the condition resulting in aortic dilation and dissection of the aorta which is fatal [9].

The close association between Turner syndrome and BAV warrants a regular cardiovascular assessment of all Turner syndrome patients to ensure early and prompt interventions, and so, knowing the prevalence of BAV in Turner syndrome patients facilitates planning this assessment process. Various studies have reported the prevalence of BAV in Turner syndrome, and one meta-analysis provided a summarized estimate, albeit with few studies combined and small sample size [10]. In this meta-analysis, we provide a more comprehensive and reliable pooled prevalence estimate of BAV in Turner syndrome and attempt to establish prevalence in sub populations of Turner syndrome such as the pure monosomy 45, X0 karyotypes and pediatric patients.

2. Materials and Methods

2.1. Search Strategies

Three reviewers independently searched PubMed, Embase, and PsycINFO databases for relevant studies on the prevalence of BAV in Turner syndrome patients. The customized search strategies for PubMed were #1. ("Prevalence" [MeSH Terms]) OR ("Occurrence" [All Fields]) OR ("Prevalence" [Title/ Abstract]) OR ("Presence of" [All Fields]), #2. ("Bicuspid aortic valve" [MeSH Terms]) OR ("Bicuspid aortic valve disease" [Title/Abstract]) OR ("BAV" [All Fields]) OR ("Bicuspid valve" [Title/Abstract]) OR ("Bicuspid aorta valve" [Title/Abstract]), #3. ("Turner syndrome patients" [MeSH Terms]) OR ("Turner syndrome" [Title/Abstract]) OR ("Turner disease" [Title/Abstract]) OR ("TS" [Title/Abstract]), #4. #1 and #2 and # 3, while those for Embase and PsycINFO were: #1. (Prevalence/exp) OR (Occurrence .ab,ti.) OR (prevalence.af.) OR (presence of .ab,ti.), #2. (Bicuspid aortic valve/exp) or ("Bicuspid aortic valve disease" .ab,ti.) OR ("Bicuspid aorta" .ab,ti.), #3. (Turner syndrome/exp) OR (Turner syndrome disorder .ab,ti.), #4. #1 and #2 and # 3.

The databases were searched in July 2021, then updated in December 2021 and February 2022. The studies were then exported into Endnote software (version 9) for cleaning, and duplicates removed. Studies from the initial search were rejected immediately if the title or abstract did not report prevalence or inci-

dence of bicuspid aortic valve disease in Turner syndrome patients. Full texts were then extracted for the remaining articles and analyzed. Manual search of all the references of the full text articles were done. Disagreements that arose during the search were all settled by consensus. Extraction of information was carried out according to the Preferred reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [11].

2.2. Inclusion and Exclusion Criteria

Relevant studies that were selected for inclusion had to meet the following criteria: 1) Assessed the prevalence of bicuspid aortic valve disease in patients with Turner syndrome; 2) BAV diagnosis was conducted using TTE or TEE or CT or MRI; 3) Had enough raw data to calculate prevalence of BAV in Turner syndrome if not already reported. Studies were excluded from the analysis if they were: case reports or case series, reviews or meta-analyses, conference abstracts or papers, did not assess the prevalence of bicuspid aortic valve disease in Turner syndrome patients, and was not published in a peer review journal.

2.3. Quality Assessment of the Studies

Three authors independently evaluated the methodological qualities of the selected studies using the Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross sectional studies [12]. Interrater reliability above 80% were considered acceptable, and all disagreements were resolved by consensus. The filled checklist is provided as supplementary materials 1. The JBI checklist assesses studies on nine critical areas that include: sample frame appropriateness, sampling technique, and sample size among others.

2.4. Data Extraction

A data extraction questionnaire was created and relevant data extracted from the included studies. Data extracted included: Name of first author, year of publication, country of the study, diagnostic tool for bicuspid aortic valve disease, summary of participants' age, number of events (BAV), total number of participants, prevalence of BAV and its calculated standard error and Turner syndrome karyotypes.

2.5. Statistical Analysis

The prevalence of BAV disease was determined as number of BAV cases over total number of Turner syndrome patents x100. Standard Error (SE) was calculated for studies that did not report them, using the prevalence data and the formula: SE = Sqrt of $p\,(1 - p)/n$, while the 95% confidence interval (CI) = $p \pm 1.96 \times \mathrm{SE}$; where, p = Prevalence. The data were combined using Review Manger (RevMan 5.4.1) and the JASP software (0.16.00). Heterogeneity was assessed using Chi-square test, and the I^2 test. Random effect model was used to pool the results. Possible publication bias was assessed by visual inspection of a funnel

plot and the Egger's test.

3. Result

Preliminary searches yielded 901 records altogether. No additional records were found from other sources. 812 of the studies were from PubMed, 83 from Embase and 6 from PsycINFO databases. Following removal of duplicates, 778 studies were left and their titles and abstracts screened for eligibility. 749 studies were then excluded and eventually 29 qualified for full text screening. Here, 14 studies were omitted; 5 did not report prevalence of BAV in Turner syndrome patients and didn't have the required raw data to manually do so, 7 were abstracts only or conference presentations and 2 were letters to the editor. Altogether, 15 studies [13]-[27] ranging from 2010 to 2020 and containing 3189 Turner syndrome patients were enrolled for meta-analysis (Table 1). The study selection and eligibility flowchart is presented in Figure 1. Among them 4 were conducted in the US, 2 from Turkey, 2 from the Netherlands, 2 from Poland and 1 each from France, Ukraine, France, Canada and Taiwan.

Table 1. Characteristics of included studies.

Author ID	Area of study	Diagnostic tool	Mean/median age of patients (Years)	Number of events (BAV)	Total number of participants (N)	Prevalence of BAV (%)	SE
Chou *et al.* 2019	Taiwan	Echo, CT, MRI	22.5 ± 5.7	6	88	6.8	0.0268
Donadille *et al.* 2012	France	Echo, MRI	25.6 (19.6 - 34.2)[1]	49	233	21.03	0.0353
Olivieri *et al.* 2013	USA	Echo, MRI	32.9 ± 15.5	47	208	22.6	0.0289
Yesilkaya *et al.* 2015	Turkey	Echo	0 - 18[3]	61	719	8.5	0.01
Bondy *et al.* 2013	USA	MRI	18.1 ± 1	57	185	31.0	0.034
Klaskova *et al.* 2017	Poland	MRI	14.0 (6.6 - 32.5)[2]	19	67	28.3	0.055
Mondal *et al.* 2020	India	Echo	14.8 ± 3.97	6	103	5.8	0.023
Yetman *et al.* 2018	USA	Echo	31.7 ± 12.6	226	569	39.7	0.02
Kim *et al.* 2010	USA	MRI	18.4 ± 6.9	20	51	39.2	0.068
Zelinska *et al.* 2018	Ukraine	Echo	9.33 ± 4.93	11	538	2.04	0.0061
Yigit *et al.* 2017	Turkey	MRI	14.3 ± 3.5	9	47	19.1	0.0573
Obara-Moszynska *et al.* 2018	Poland	MRI, Echo	13.9 ± 2.2	16	39	41.0	0.076
Duijnhouwer *et al.* 2018	Netherlands	MRI, CT	28.7 (21.3 - 39.7)[1]	59	268	22.0	0.0253
Bons *et al.* 2018	Netherlands	CT	35 ± 13	12	50	24.0	0.06
Somerville *et al.* 2016	Canada	MRI	13.3 (9.0 - 17.9)[2]	9	24	37.5	0.0988

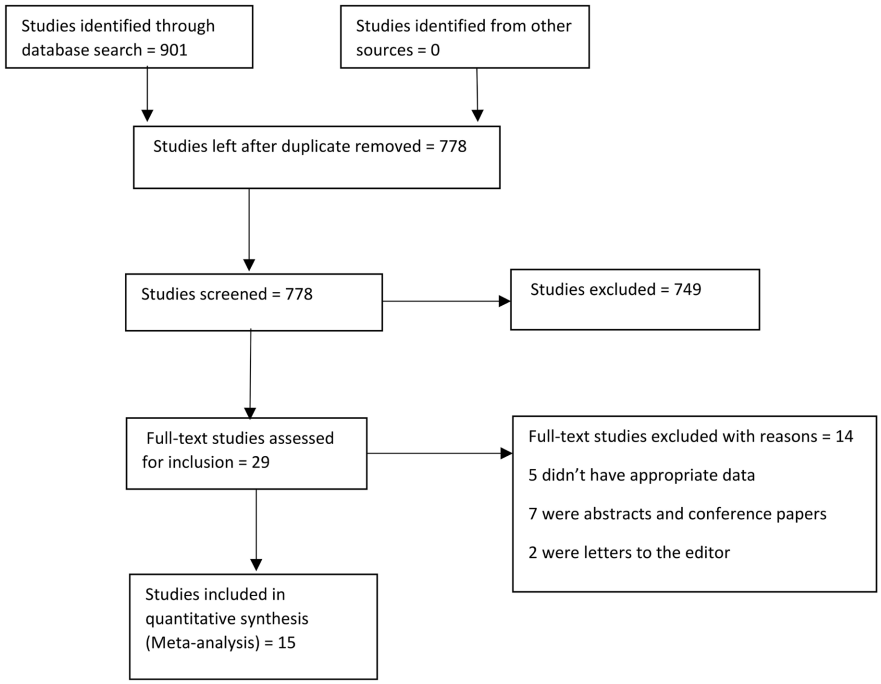

Figure 1. Study selection flowchart.

From among the included studies, the prevalence of Bicuspid Aortic Valve disease (BAV) among Turner syndrome patients was between 2.04% to 41.0%. The pooled prevalence after meta-analysis was 22.0% [95% CI: 15.0% - 29.0%], (**Figure 2**). Studies varied widely as indicated by the high level of heterogeneity, I^2 = 97% (P < 0.00001). Possible publication bias was determined by visual inspection of a funnel plot (**Figure 3**), and an Egger's test conducted (**Table 2**). Four studies determined the prevalence of BAV by Turner syndrome karyotype. Monosomy 45x karyotype had the most frequent cases of BAV compared to others. A subgroup analysis of the four studies conducted by Turner syndrome karyotype showed a pooled prevalence of 24.0% [95% CI: 9.0% - 39.0%] among the Monosomy 45x patients (**Figure 4**). Similarly, three studies explicitly studied BAV among children with Turner syndrome aged 0 to 18 years. Pooled prevalence in these studies was 8.0% [95% CI: 2% - 15%] (**Figure 5**).

4. Discussion

In this study, we have provided a summary estimate of the prevalence of Bicuspid aortic valve disease (BAV) in Turner syndrome patients. We have pooled published studies up to 2022, without any time constraints, as a result, our study had a combined total of 3189 patients, adequately powering the study. This is a comprehensive assessment of studies conducted on BAV in Turner syndrome patients, hence giving a more robust and reliable estimate of the prevalence of BAV in Turner syndrome. In addition, we were able to conduct subgroup analyses for age and Turner syndrome karyotypes to account for the heterogeneity that existed among the individual studies. Our pooled prevalence indicates that

close to a quarter of Turner syndrome patients (22%) develop BAV, while the prevalence were 24.0% and 8% for 45, X0 karyotype, and pediatrics respectively.

This result is comparable to a similar study conducted by Li *et al.* [10], who found a prevalence of 23.7%. Unlike their study however, ours is more comprehensive and highly powered; with a sample size three times theirs. This makes our study more robust and reliable. Furthermore, unlike theirs, our study evaluated prevalence of BAV in Tuner syndrome patients with 45, X0 karyotype (being the most common karyotype), and among pediatrics, since BAV is a congenital disease.

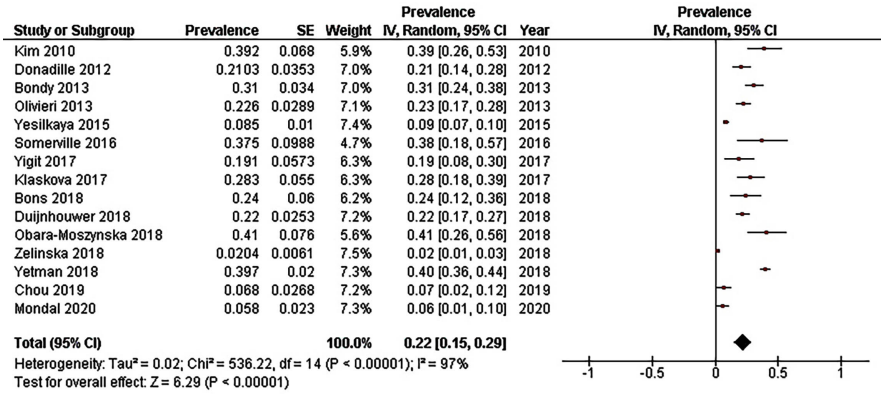

Figure 2. Forest plot of the pooled prevalence of BAV in Turner syndrome patients.

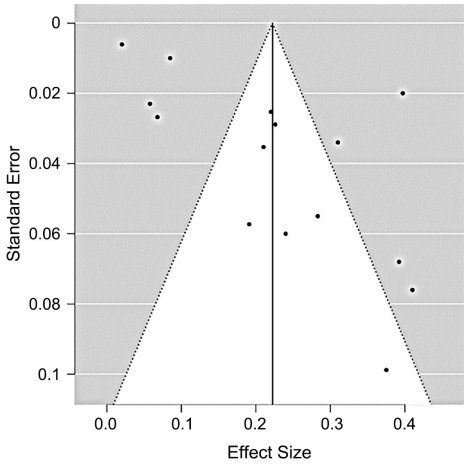

Figure 3. Funnel plot indicting possible publication bias shown by the lack of symmetry.

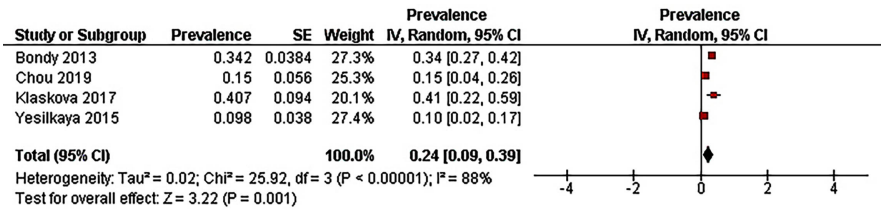

Figure 4. Forest plot showing prevalence of BAV in true monosomy 45, X0 Turner syndrome patients.

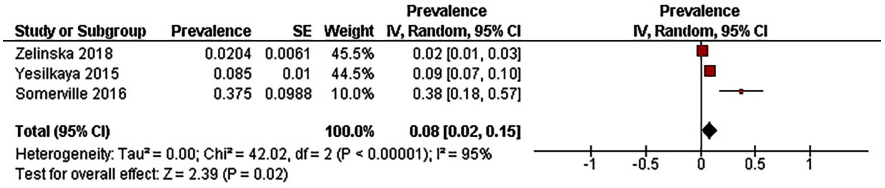

Figure 5. Forest plot of prevalence of BAV in pediatric Turner syndrome patient.

Table 2. Regression test for Funnel plot asymmetry ("Egger's test").

	z	p
sei	2.926	0.003

The possible association between Turner syndrome and cardiovascular defects including BAV has been demonstrated by a number of studies [13]-[28], as a result, vasculopathy is often seen as one of the defining features of Turner syndrome [29]. Cardiovascular complications are of particular concern to Turner syndrome patients because factors that promote cardiovascular diseases such as obesity, hyperlipidemias, atherosclerosis etc. are also quite common among Turner syndrome patients [30]. Malformation of the aortic valve is manifested in changes to the way blood flows in the ascending aorta, and is one of the causes of aortic dilation and dissection [31]. Our findings—showing that close to 1 in 4 Turner syndrome patients had BAV—reinforces the 2016 recommendation by Gravholt *et al.* [28], that all Turner syndrome patients should be routinely examined for BAV. However, in the course of this routine examination, emphasis should be put on 45, X0 karyotype patients, since by our results, they seem to have a higher prevalence of BAV than the other karyotypes. Other cardiovascular defects associated with BAV and Turner syndrome that should be equally checked include; aortic coarctation, elongated transverse aorta, and partial anomalous pulmonary venous connection [21].

Despite the frequent presence of mosaicism among Turner syndrome karyotypes, true monosomy X having the 45, X0 still accounts for an estimated 40% - 50% of all cases [32]. In our analysis, the pooled prevalence of BAV among the 45X, X0 karyotype (24%) was just slightly above that of the general Turner syndrome population. This however, was an estimate from only four of the studies that had data for the association. We therefore think the true estimate could be much higher if more studies had data on this association. BAV is a congenital heart defect that is often asymptomatic in the general population, sometimes until adulthood [8]. This is not the case with Turner syndrome where the risk developing symptomatic BAV right from childhood is exacerbated by other associated cardiovascular complications. Our pooled prevalence of BAV in pediatric Turner syndrome patients was 8% from three studies. Much as echocardiography is the diagnostic tool of choice in BAV, it is not entirely sensitive enough and may miss cases especially in children. Bondy *et al.* and the Turner syndrome study group advised that Cardiac Magnetic Resonance Imaging (CMR) be done

for all pediatric patients who can be imaged without sedation whose Echocardiogram results are negative [33]. Similar remarks form a study conducted specifically in pediatric subjects by Somerville *et al.*, reaffirmed this suggestion as CMR was able to detect BAV cases that were missed by Echocardiogram [27].

Limitations

Being mostly retrospective cross sectional studies, we could not rule out potential biases among the individual studies. In fact both the funnel plot and Egger's test conducted showed possible publication biases. Secondly, the studies were quite heterogeneous hence somehow affecting generalization of the result. Lastly, most of the studies did not evaluate BAV prevalence by Turner syndrome karyotype, and so the sub group analysis by karyotype should be interpreted with caution.

5. Conclusion

In summary, this study found that the prevalence of BAV in patients with Turner syndrome is 22% and that by karyotype, 24% of true monosomy 45, X0 develop BAV, while 8% of pediatric patients develop the complication. With a sample size of 3189, this is a more reliable estimate of the prevalence of BAV in Turner syndrome patients. Given that 1 in 4 Turner syndrome patient is likely to have BAV according to this result, and that true monosomy 45, X0 karyotypes seem to have a higher prevalence than the rest, particular attention should be put on patients with true monosomy 45, X0 karyotypes in the course of routine screening for BAV and other cardiovascular diseases in Turner syndrome patients. Lastly, where possible, CT and MRI should always accompany echocardiography for BAV screening, especially in pediatric patients.

Author Contributions

"Conceptualization: Erick Thokerunga; methodology: Erick Thokerunga; software: Erick Thokerunga; validation: Erick Thokerunga; formal analysis: Erick Thokerunga and Yahya-Abdullahi Ali; data curation: Yahya-Abdullahi Ali and Erick Thokerunga; writing-original draft preparation: Erick Thokerunga; writing-review and editing: Yahya-Abdullahi Ali and Christopher Ntege; supervision: Christopher Ntege; funding acquisition: Christopher Ntege. All authors have read and agreed to the published version of the manuscript".

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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