A Meta-Analysis and Systematic Review of Anatomical Variations in ihe Drainage Pattern of the Azygos Venous System

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ABSTRACT

Introduction: The azygos venous system drains blood from the upper lumbar region of the abdomen and thoracic wall. It includes the azygos vein laying on the right and its left side counterparts, the hemiazygos, and accessory hemiazygos veins. The azygos vein receives all the right side posterior intercostal veins. The hemiazygos and accessory hemiazygos veins empty into the azygos vein after receiving the left side posterior intercostal veins. The azygos venous system shows variable drainage pattern in the posterior thorax.

Objective: The main aim of this systematic review and meta-analysis was to determine the pooled prevalence of each of the azygos venous system drainage pattern types.

Method: PubMed, Scopus, Science Direct, and Google Scholar were searched extensively. The prevalence of each drainage pattern and other relevant data were extracted and organized in a Microsoft Excel spreadsheet. Stata/SE 14 software was employed to estimate the pooled prevalence of the four different types of azygos venous system drainage patterns. Heterogeneity was checked by a forest plot. Funnel plots and Egger's test were done to assess publication bias. Subgroup analysis was done based on the geographic location of studies.

Result:A total of nine articles conducted using 588 human cadaveric specimens were included in the meta-analysis and systematic review. Type II (Transitional) was the most prevalent drainage pattern of the azygos venous system with a prevalence of 81.83% (95% CI: 66.71, 96.95). The other variant types were: Type I (Primitive or Embryological) (10.85%), Type III (Unicolumnar) (3.41%), and atypical (7.13%).

Conclusion: A considerable variability in the drainage pattern of the azygos venous system was noted. Transitional type was the most prevalent drainage pattern of the azygos venous system with a prevalence of 81.83%.

Key Words: *Azygos Venous System; Drainage Pattern; Anatomical Variation; Meta-Analysis*

INTRODUCTION

The azygos venous system in the thorax is responsible primarily for draining venous blood from the thoracic wall to the superior vena cava (SVC). The term azygos means "unpaired" and describes the asymmetry in this venous system. The azygos vein (AV) on the right, as well as the hemiazygos vein (HV) and accessory hemiazygos vein (AHV) on the left, make up the azygos system of veins. Both the AV and the HV are formed from the lumbar veins ascending from the abdomen uniting with the subcostal vein [1].

On the right, the AV is continuous, collecting blood from the right intercostal veins before arching over the root of the lung to join the SVC. It receives blood from the bronchial, pericardial, and right superior intercostal veins; the posterior right intercostal veins from the fifth to eleventh intercostal spaces; the superior phrenic, mediastinal, and esophageal veins; and the vertebral venous plexuses [2].

Apart from the drainage of the structures in the posterior mediastinum, the azygos systems of veins serve as a collateral circulation by forming cavo-caval and porto-caval junctions during caval vein occlusion and portal hypertension [3-5]. The azygos system veins vary greatly in their mode of origin, course, tributaries, anastomoses, termination, and drainage pattern.

An effort has been done to classify the different variable arrangements of the azygos venous system by different researchers. Two of the most commonly accepted classification schemes by many anatomists are the work of Anson B.J. [6] and Seib G.A. [7]. In his study of 100 cadavers, Anson B.J. classified the azygos venous system vertical and horizontal connections into 3 types (primitive or embryological, transient, unicolumn) and 11 groups (Table 1). Similarly, Seib G.A. classified the azygos venous system pattern into three types (double column, transitional, and single column). However, unlike to Anson B.J., Seib G.A. divided the three types into 21 groups.

Type I (Primitive or Embryological): It is a primitive or embryological form consisting of two separate veins lying parallel to each other in the posterior mediastinum, being anterior and lateral to the vertebral column. These

TABLE 1

Anson B.J. classification of the azygos venous system drainage pattern.

Group	Description
1	Type I (Two separate veins lying parallel to each other in the posterior mediastinum)
2	There is one midline horizontal connection between the right and left trunk, usually at the level of T8.
3	There is one horizontal connection between the right and left trunk above T8.
4	There are two horizontal connections between the right and left trunk, superior horizontal connection at T8 and inferior horizontal connection below the level of T8.
5	There are three to five horizontal connections between the right and left trunk.
6	The trunk of the left side is broken once. This group is again divided into i) Group 6A, where there is a connection between accessory hemiazygos vein and left brachiocephalic trunk vein and ii) Group 6B, where there is no connection between accessory hemiazygos vein and left brachiocephalic vein.
7	There are two breaks in the left trunk.
8	There is one break in the left trunk, above and below the break; posterior intercostal veins are joined by collaterals.
9	There are 5 breaks in the lower part of the left trunk, and two single veins, in the lower part formed by joining of 11th and 12th intercostal vein and 10th and 9th intercostal vein.
10	There are 5 breaks in the lower part of the left trunk
11	Type III (It has a single azygos vein that lies on the anterior surface of the vertebral column)

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parallel veins are the AV at the right side and the continuous superior and inferior HV on the left side. The vein at the right side and left side empties into the SVC and the left brachiocephalic vein, respectively. This type is also named as group 1. It was seen only in 1% of the 100 specimens examined by Anson B.J. [6].

Type II (Transitional): It has at least one retro-aortic anastomosis between the azygos and hemiazygos venous systems. 98% of the 100 specimens studied by Anson B.J. are in this form. Based on the number of retro-aortic communications it was further divided into nine subgroups, denoted as groups 2-10 [6].

Type III (Unicolumnar): This type has a single AV that lies on the anterior surface of the vertebral column. It is also named as group 11. It was found only in 1% of all the cases seen by Anson B.J [6,7].

Variations of the azygos venous system may be wrongly interpreted by radiologists as aneurysm, tumor, lymphadenopathy, or other abnormalities while reporting radiological examinations of the posterior mediastinum [3,4]. Venous abnormalities often complicate mediastinal surgery with intraoperative hemorrhage. Accidental damage to large vessels may have life-threatening consequences. Prior knowledge of possible anatomical variants may help the surgeon reduce the risk of such events.

Therefore, a Cardiothoracic surgeon should anticipate for the presence of azygos venous system variations to prevent intrathoracic hemorrhage during operative procedures involving the posterior mediastinum [3]. Moreover, there is no consensus between standard anatomy books as well as other literature regarding the drainage pattern of the azygos venous system.

The main aim of this systematic review and meta-analysis was to establish the overall prevalence of variations in the formation, course, termination and drainage pattern of the azygos venous system.

METHODS

THE SEARCH STRATEGY: The major online databases, including PubMed, Scopus, Science Direct, and Google Scholar were searched extensively up to November 30, 2019 to collect all eligible articles reporting prevalence data on variations in azygos venous system drainage patterns. Date range restrictions were not employed. After the initial search, articles that were included were also reference searched. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were strictly followed (PRISMA).

ELIGIBILITY ASSESSMENT: All observational (cadaveric or imaging) studies that reported relevant and extractable data on anatomic variations of the azygos venous system conducted anywhere in the world were included. Articles published only in the English language were considered for inclusion. Both published and unpublished studies were included.

The exclusion criteria used were:

1. Articles with no relevant information or reported incomplete data needed for analysis;

2. Case reports, case series, letters to the editor, review articles, and conference abstracts;

3. Articles that was not fully accessible after waiting two weeks of formal email request of the corresponding authors

DATA EXTRACTION: Data were extracted from each included article using a standardized data extraction format by two authors (MJ and GS) independently. Differences in data between the extractors were discussed until consensus was reached. For each study included, data about the primary author, sample size, study type, country, and the prevalence of each drainage pattern was extracted.

STATISTICAL ANALYSIS: Statistical analysis was performed using Stata version 14/SE to calculate the pooled prevalence estimates of the four types of the azygos venous system drainage patterns. All of the analyses were performed by using a random-effects model due to an anticipated heterogeneity [8]. Cochran's Q chi-square and I2 values were used to assess heterogeneity [9]. For all analyses, $P<0.05$ was assumed to be statistically significant.

In order to check possible publication bias subjectively, a funnel plot was done using metafunnel command of Stata 14. Egger's test [10] was also done by running metabias command in Stata for the same outcomes.

The presence of significant heterogeneity between the studies demanded the need to perform subgroup analysis. Subgroup analysis was done by study continent to estimate the pooled prevalence of each of the four types of azygos venous system drainage patterns.

RESULT

STUDY IDENTIFICATION

A search of all the major medical databases yielded a total of 1650 articles. 108 articles were selected for screening after removing 94 duplicate and 1448 irrelevant records. After excluding articles lacking extractable data, case reports, letters to editors, and containing nonhuman data, 29 full texts were assessed for eligibility. Finally, 9 studies that satisfied the inclusion criteria were included in the review.

CHARACTERISTICS OF INCLUDED STUDIES

A total of 9 studies were included in this systematic review and meta-analysis. A description of the characteristics of the included studies is shown in (Table 2). The articles ranged in date from 1934 to 2019. A total of 588 cadaveric specimens were included in the review. The specimens represent about three continents of the world; the majority being from the USA (300) followed by Asia (258), and Europe (30).

The meta-analysis result of the 588 included specimens showed the commonest azygos venous system to be the transitional type with a prevalence of 81.83%. The second commonest pattern was the primitive or embryological type (10.85%). Unicolumn type was a rare variant with a prevalence of only 3.41% (Table 3). Forest plots of the four different arrangements are shown in to 7. Azygos venous system patterns that do not match either of the three types were categorized as Atypical.

Although nine studies were included in the meta-analysis, one study from Type I and three studies from Type III did not appear in the forest plot since the software excludes studies having a prevalence of 0% and 100%.

Of the nine studies included, only five studies provided data about each group of Type II pattern. Accordingly, group 3 was found to be the commonest pattern (Table 4).

TABLE 2

Description of the studies included in the systematic review and meta-analysis.

Author	YearPublished	Country	Study type	No of specimens
Stelina Sophie (11)	2015	India	Cadaveric & Imaging	50
Dahran and Soames(12)	2016	Scotland	Cadaveric	30
Rao and Banjere (13)	2014	India	Cadaveric	40
Prasad (14)	2013	India	Cadaveric	50
Rao and Banjere (4)	2016	India	Cadaveric	60
Patra et al (15)	2017	India	Cadaveric	30
Kutoglu T (16)	2011	Turkey	Cadaveric	48
Seib GA (7)	1934	USA	Cadaveric	200
Falla A (17)	1963	USA	Cadaveric	100
Total				588

TABLE 3

Prevalence of the four-azygos venous system drainage pattern types, a meta-analysis of nine studies, n=588.

	Type I	Type II	Type III	Atypical
Prevalence % (CI)	10.85 (0.33, 31.36)	81.83 (66.71,96.95)	3.41 (1.01, 5.81)	7.13 (-2.10, 12.16)
I2 in %	97.2	97.1	41.1	60.8

TABLE 4

Prevalence of Type II subgroups.

Group	Prevalence(95% CI)	I^2	P-value
2	17.36 (9.88, 24.84)	41.3	0.146
3	18.17 (3.37, 32.97)	89.5	0.0
4	17.63 (10.22, 25.03)	37.7	0.170
5	13.69 (19.20, 20.19)	35.6	0.184
6A	6.85 (1.86, 11.84)	0.0	0.454
6B	13.97 (2.78, 25.17)	68.97	0.040
7	17.54 (5.34, 29.34)	66.3	0.051
8	No case		
9	3.11 (-0.93, 7.16)	0.0	0.341
10	5.57 (-0.03, 11.17)	0.0	0.84

Note: No case in group 8 does not mean there is no such azygos venous system arrangement. Rather, it should be noted that it was not observed in the five studies that reported data about groups of azygos venous system pattern.

TABLE 5

Subgroup analysis of the prevalence of the four-azygos venous system drainage pattern types by continent.

Continent	Type I prevalence	Type II prevalence	Type III prevalence	Atypical
Asia	3.91 (1.29, 6.52)	86.99 (82.66, 91.33)	3.41 (0.01, 6.81)	7.13 (-2.10, 12.16)
Europe	3.33 (-3.09, 9.75)	86.67 (74.51, 98.83	10 (-0.74, 20.74)	0
North America	29.40 (-26.46,85.26)	67.58 (7.80, 127.36)	2.83 (-1.08, 6.73)	0
Overall	10.85 (0.33, 31.36)	81.83 (66.71, 96.95)	3.41(1.01, 5.81)	0

PUBLICATION BIAS

The funnel plots are more or less symmetrical in three of the four arrangements (Type I to III) indicating the absence of publication bias. To make it objective Egger's test was also done and showed the absence of significant bias in Type I (p=0.246), Type II (p=0.275), and Type III (p=0.074). However, Egger's test showed a significant asymmetry in atypical arrangement (p=0.033).

SUBGROUP ANALYSIS

The subgroup analysis of the azygos venous system drainage patterns showed variation by study continent. The highest prevalence of Type I pattern was seen in North America (29.4%), while the lowest was seen in Europe (3.33%). Type II pattern was almost equally high in Asia and Europe. Type III pattern was higher among the Europeans (Table 5). All the atypical patterns observed were found from Asian studies.

DISCUSSION

This meta-analysis is aimed to provide anatomic insights into the different variants of the azygos venous system from its formation to its termination. The review is the first one that uses statistical methods to assess the prevalence of anatomical variants in the arrangement of the azygos venous system. The differences are almost at the individual level because of the different division, adjunction, and closure of several longitudinal and transverse embryological veins. It is more common in the left side representatives; the AHV being the most variable.

Four different types of azygos venous system arrangements were identified and their pooled prevalence was estimated using Stata/SE 14 software. Type II arrangement was the most common followed by Type I. Type III was the least common type [11-14].

The variations in the arrangement of the azygos venous system can be explained by its complex embryologic origin. As shown in, largely, the AV develops from the upper portion of the right supra-cardinal vein. The azygos arch portion (terminal part); however, develops from the persistence of the cranial end of the right posterior cardinal vein. The HV and AHV develop from the upper segment of the left supra-cardinal vein [7,15,16,17-24]. The retro-aortic connection of the right and left azygos lines develops from the persistence of the embryologic communication between the right and left supra-cardinal veins [3,19,20].

An independent right and left side azygos venous system will be observed when the embryologic form persists without trans-vertebral communication. This type of azygos venous system pattern results due to the regression or absence of subcentral veins and the persistence of the left azygos line vein [18]. In the overall analysis, such type of pattern was encountered in 10.85 % of the specimens. Anson B.J. categorized this arrangement as Type I having only one subtype (Group 1). In the study of Anson B.J., Type I pattern was seen in a relatively small number of specimens (1%) compared to the current meta-analysis.

This meta-analysis showed an overall Type II azygos venous system drainage pattern prevalence of 81.83%. Although this form is the commonest type, its prevalence is lower than the finding of Anson B.J. (98%) [6]. Embryologically, Type II azygos venous system drainage pattern occurs when the usual pattern (normal development of cardinal vein) is present.

As stated in Anson's system of classification, the Type II pattern has nine subtypes (Groups 2-10). Group 3 subtypes was found to be the commonest of all the Type II divisions in this meta-analysis followed by Groups 4 and 7. The first four subtypes of Type II (Groups 2-5) differ by the number of retro-aortic transverse connections between the right and left azygos lines. The number of retro-aortic connection increases from Group 2 to Group 5.

These retro-aortic transverse connections result from the persistence of embryological connections between the right and left supra cardinal veins [4]. As shown in, the hemiazygos and AHV become connected and form one vertical channel in Groups 2-5. Embryologically, this can be explained by the persistence of complete left supra cardinal vein [3,20].

Between Groups 6 and 10, there is at least one break on the left side trunk. The number of breaks gradually increasesfrom Group 6 to Group 10. As opposed to Groups 2-5, there is no connection between the hemiazygos and the AHV in Groups 6 to 10. The possible explanation for such subtype is nondevelopment of the left supra cardinal vein in areas where breaks are seen. Group 6 is divided into 6A and 6B based on the presence or absence of connection between the AHV and left brachiocephalic vein. As shown in, the connection is present in 6A and absent in 6B.

The HV and AHV could be absent or poorly developed. The AV receives the left posterior intercostal veins directly in the absence of the HV, AHV or both. When both of the left side representatives are absent, the AV lies in the midline and receives the posterior intercostal veins of both sides. This type was seen in 3.41% of the specimens in this meta-analysis. Based on Anson's system of classification, this form is classified as Type III. Such arrangement of the azygos venous system results due to complete regression of the upper segment of the left supra-cardinal vein [16,18,20].

CONCLUSION

The pooled prevalence of the four types of azygos venous system drainage patterns (embryological, transient, unicolumn, and atypical) showed the transitional type to be the commonest. The highest prevalence of Type I and Type III patterns were observed in North America and Europe, respectively. All the atypical patterns observed were found from Asian studies.

The finding of this meta-analysis will support the teaching of students and the training of professionals. The number of specimens examined by the studies included in the current meta-analysis are small as most of the studies used cadavers. To better understand racial variations, authors recommend further radiologic imaging studies to include the African population.

LIST OF ABBREVIATIONS

AHV: Accessory hemiazygos vein; AV: Azygos vein; CT: Computerized tomography: CI: Confidence interval; HV: Hemiazygos vein; IVD: Intervertebral disc; T: Thoracic vertebra; USA: United States of America

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AUTHORS' CONTRIBUTIONS

MJ developed the protocol and design of the study. MJ and GS performed the article searching, data extraction, and analysis. MJ was a major contributor in writing the manuscript. GS reviewed and assessed the quality of the manuscript. All authors read and approved the final draft.

CONFLICTS OF INTERESTS

The authors declare that they have no competing interests

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