A meta-analysis of the prevalence of biliary anatomical variants: development of a comprehensive prevalence-based classification system

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INTRODUCTION

Liver resection is the gold standard treatment for primary liver malignancies and selected liver metastatic disease. Advances in surgical and anaesthetic techniques allowed surgeons to perform complex hepatic resections with low mortality[1] and paved the way for advances in living donor liver transplantation (LDLTs), which has seen a substantial increase in certain parts of the world. Thorough understanding and preoperative knowledge of liver anatomy, including anatomical variants of vasculature and biliary system is paramount[2]. Complications that arise when a surgeon is unaware of their existence can be severe with adverse impact on patient outcomes[3,4]. Historically, anatomical biliary variants (ABVs) were often underappreciated and the prevalence is inconsistently reported in the literature. To address this, we performed a systematic review and meta-analysis to provide a comprehensive overview of ABV distribution. Furthermore, we constructed a prevalence based, clinically relevant classification system, that highlights the prevalence of surgically relevant ABVs.

METHODS

This systematic review was performed and reported according to PRISMA guidelines[5]. Data was retrieved from MEDLINE and EMBASE until the 9th of September 2019. Our search strategy is detailed in supplementary table S1. Literature was considered eligible for inclusion if it was: A) published original research, B) classifying biliary variants according to the first four or first five variants as shown in figure 1, C) using data from unselected patients. From included studies, country of publication, year of publication, visualisation method, classification method, population, and classification distribution, were collected. Literature selection and data collection were completed independently by two assessors (B.J., S.v.L.) with discrepancy resolved by discussion. No a-priori review protocol was registered.

Data were converted to a single classification system based ABV prevalence (figure 1) and the commonly used classification systems[6-9]. Supplementary table S5 details how the other commonly used classifications overlap our proposed system. Because not all studies reported the presence of the variant in which the cystic duct (CD) joins the right sectoral duct (RSD) (5th variant), the primary analysis focuses on four anatomical variants. For this analysis, variants other than these four were categorized as 'other'. To assess the prevalence of the 5th variant, we performed a separate analysis of studies reporting on the 5th variant. We also performed populational analyses categorizing studies into ethnic/regional subgroups based on a previously reported system[10,11], which are detailed in supplementary table S2. Regional subgroups were assigned based on the location of the study groups.

A multinomial logistic mixed effect model, with study heterogeneity captured by a random intercept, was used to estimate the overall proportion of each anatomical type across all studies. Ninety-five percent confidence intervals were used for the estimated proportion of each anatomical type using a parametric bootstrap with 10,000 repetitions. Here, parametric bootstrapping (Efron, 1985) is a technique that uses the estimated distribution (i.e. multinomial mixed-effect logistic model) to generate additional synthetic data in order to estimate the confidence intervals of parameter estimates. For homogeneous studies, a multinomial logistic regression without random effects was used to obtain both the estimated proportion and associated confidence intervals. Analyses were performed using custom code written in R (v 3.6.0).

RESULTS

Our search identified 2443 studies. After removal of duplications, 1709 studies remained and a further 1640 were excluded due to non-relevance. Of the remaining 69 studies, 34 were considered eligible for inclusion. By assessing the references in these 34 studies, 3 more studies were included. This resulted in a final inclusion of 37 studies, covering a population of 12684. Supplementary figure 1 provides a PRISMA flow chart for article inclusion. Table 1 shows the data generated from each included study and supplementary table S3 provides the references of included articles.

The main meta-analysis, based on 12684 patients, showed estimated average ABV proportions of type 1 of 65.9%, type 2 of 14.2%, type 3 of 11.7%, type 4 of 6.5%, and 'other' group proportion of 1.7%. Twenty-one studies (n=8204) reported on the ABV type 5, for which meta-analysis showed a proportion of 0.6%. All ABV types are shown in Figure 1. Within the 'East-Asia' region (n=5683), the estimated average ABV type 1 proportion is 69.6%, type 2 is 10.8%, type 3 is 12.0%, type 4 is 6.3% and 'other' group type is 1.2%. Within the 'Europe, North-America & Oceania' region (n=324), the estimated average ABV type 1 proportion is 59.3%, type 2 is 17.6%, type 3 is 12.7%, type 4 is 10.0% and 'other' group type is 0.5%. Within the 'Mediterranean-Basin' region (n=273), the estimated ABV type 1 proportion is 64.9%, type 2 is 14.3%, type 3 is 12.8%, type 4 is 6.6% and 'other' group type in 1.5%. Within the 'Middle-East & North-Africa' region (n=5882), the estimated average ABV type 1 proportion is 63.5%, type 2 is 16.1%, type 3 is 11.2%, type 4 is 6.2% and 'other' group type is 2.8%. Within the 'South-Asia' region (n=522), the estimated average ABV type 1 is 56.9%, type 2 is 21.8%, type 3 is 9.6%, type 4 is 5.6% and 'other' group type is 6.1%. Supplementary table S4 details the results from the meta-analyses.

DISCUSSION

In our new prevalence-based classification system, type 1 is characterized by the RPSD joining the RASD forming the RHD. This is considered standard anatomy and is found in 65.9% of the population. This ABV should not pose a problem during surgical interventions. Type 2 where the RASD/RPSD (2A/2B) drains into the LHD, is found in 14.2% and is relevant during left hepatectomy and LDLT involving right lobe. Type 3, the trifurcation of the RASD, RPSD and LHD, is found in 11.7%, and also relevant during LDLT setting. In type 4 the RPSD that drains into the CHD, found in 6.5%, and is commonly referred to as a low insertion of the RPSD, and is relevant in cholecystectomies where it can be mistaken for the CD. Type 5 is characterized by the RPSD into which the CD drains, is found in 0.6%, and is crucial in cholecystectomies where it can be inadvertently injured if mistaken for CD. 'Other' ABVs represent 0.5% of variants which do not fit in the first 5 types.

Our novel classification has advantages over the existing systems. First, it aims to inform uniform reporting of intrahepatic biliary anatomy, creating a common ground for clinicians to clearly convey the presence of ABVs. Secondly, it focuses on clinical implications of ABVs with naming of distinct, prevalent ABV groups that have impact on surgical intervention, and is therefore clinically useful. This simplifying of variants based on prevalence and clinical implication is aimed at making our classification system comprehensive yet simple to use. Further, we devised our system by amalgamating the merits of previously described classification systems.

Several population differences appear to exist. When comparing the 'East-Asia' population to the 'Middle-East and North-Africa' population, type 1 seems more common whilst type 2 is less common in 'East-Asia'. Insight into the distributions of variants between populations serves as an aid for surgeons in their respective localities to benefit from our novel classification system.

We acknowledge the limitations of our findings. First, whilst the overall estimates are likely accurate representations of the underlying averages, subgroup analyses are less robust as the study size gets considerably smaller in subgroups. Second, heterogeneity within subgroups suggest that other influencing variables may exist and have not fully assessed (e.g. gender, multiple ethnic origins within a study sample). As our regional subgroup classification is based largely on geography, it does not take into account the multi-ethnic nature of studied populations. Therefore, there is potential for bias.

This systematic review provides the most comprehensive overview of intrahepatic biliary anatomical variants to date. We highlight the presence of regional differences. Additionally, we propose a clinically focused, prevalence-based classification system based on meta-analysis of a large pooled dataset whilst incorporating the merits of previous classification systems.

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FIGURES

Figure 1. Prevalence based classification system of anatomical biliary variants (ABVs)

[Image excluded because of file size (146MB**)]**

Legend: RA = right anterior, RP = right posterior, R = right hepatic duct, L = left hepatic duct, CHD = common hepatic duct

TABLES

Table 1. Included literature and proportions of anatomical biliary variants (ABVs)

Author	Country of publication	Region	Year of publication	Visualisation method	Population (n)	Type 1 (n)	Type 2 (n)	Type 3 (n)	Type 4 (n)	Other (n)	
										Type 5	Other
Yoshida et al.	Japan	EA	1996	Cholangiography	1094	739	88	194	66	5	2
Huang et al.	Taiwan	EA	1996	Unknown	958	600	105	182	56	15	0
Cheng et al.	Taiwan	EA	1997	Cholangiography	210	137	31	35	6	1	
Kim et al.	South-Korea	EA	2002	Cholangiography	532	403	29	58	42	0	0
Nakamura et al.	Japan	EA	2002	Cholangiography	120	78	19	11	10	2	
Choi et al.	South-Korea	EA	2003	Cholangiography	300	197	38	32	19	6	8
Kitagawa et al.	Japan	EA	2003	Cholangiography	180	113	26	36	5	0	
Limanond et al.	USA	ENAO	2004	Cholangiography and MRCP*	26	19	1	5	1	0	0
Ohkubo et al.	Japan	EA	2004	Surgical specimen	110	80	13	6	5	6	
Varotti et al.	USA	ENAO	2004	Cholangiography	77	43	16	11	7	0	
Chen et al.	USA	ENAO	2005	MDCT cholangiography	56	33	10	7	5	1	
Wang et al.	USA	ENAO	2005	CT cholangiography	62	35	11	7	9	0	
Song et al.	South-Korea	EA	2007	Cholangiography and MRCP*	111	67	8	9	22	2	3
Sirvanci et al.	Turkey	MENA	2007	Cholangiography and MRCP*	62	43	9	6	3	0	1
Karakas et al.	Turkey	MENA	2008	MRCP	112	61	24	16	11	0	0
Cucchetti et al.	Italy	MB	2011	Cholangiography	200	129	24	28	16	3	
Kim et al.	South-Korea	EA	2011	Cholangiography	875	492	108	227	43	5	
Abdelgawad et al.	Egypt	MENA	2011	MRCP	20	16	2	1	1	0	
Tawab et al.	Turkey	MENA	2012	MRCP	106	67	18	11	8	2	0
Yaprak et al.	Egypt	MENA	2012	Cholangiography and MRCP	200	126	37	12	16	1	8
Barsoum et al.	Egypt	MENA	2012	MRCP	50	30	15	3	2	0	0
Mariolis-Sapsakos et al.	Greece	MB	2012	Cadaveric	73	48	15	7	2	1	0
Thungsuppawattanakit et al.	Thailand	EA	2012	MRCP	163	106	15	28	9	5	
Lyu et al.	Taiwan	EA	2012	MRCP	465	307	60	42	41	15	
Uysal et al.	Turkey	MENA	2014	MRCP	1011	803	42	81	73	12	
Deka et al.	India	SA	2014	Cholangiography	299	173	52	24	20	7	23
Al-Jiffry et al.	Saudi-Arabia	MENA	2015	Cholangiography	177	104	31	19	12	2	9
Takeishi et al.	Japan	EA	2015	CT cholangiography	407	306	37	39	25	0	
Nayman et al.	Turkey	MENA	2012	MRCP	2143	1329	245	202	149	1	217
Taghavi et al.	Iran	MENA	2016	ERCP	362	163	48	78	13	0	60
Sarawagi et al.	India	SA	2016	MRCP	223	124	62	26	9	2	0
Hussein et al.	Egypt	MENA	2016	Cholangiography	248	150	44	28	16	3	7
Kitami et al.	Japan	EA	2016	CT cholangiography	158	123	19	8	5	3	
Adatape et al.	Turkey	MENA	2016	MRCP	1041	693	126	133	52	37	
Bauschke et al.	Germany	ENAO	2017	Cholangiography and MRCP	103	67	17	15	2	2	
Ulger et al.	Turkey	MENA	2018	MRCP	200	103	49	24	16	8	
Al-Muhanna et al.	Saudi-Arabia	MENA	2019	ERCP and MRCP	150	84	43	20	2	1	0

Abbreviations: EA = 'East Asia', ENAO = 'Europe, North America & Oceania', MB = ' Mediterranean Basin', MENA = 'Middle East & North Africa', SA = 'South Asia', MRCP = Magnetic resonance cholangiopancreatography, MDCT = Multiple detector computed tomography, CT = Computed tomography. *Cholangiogram data is extracted for studies that provide data on both cholangiogram and MRCP.

SUPPLEMENTARY MATERIAL

Supplementary table S1. Search overview

Search overview	**Results (n)**
Databases used	
- Ovid MEDLINE between 1946 and September 09, 2019.	
- Ovid EMBASE between 1974 and September 09, 2019.	
Search strategy for both databases	
1. Bile duct.mp. or exp Bile Ducts/	
2. Biliar*.mp.	
3. (Bile* adj3 (Tract* or Tree*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
4. variat*.mp.	
5. variant*.mp.	
6. exp Anatomic Variation/ or variation.mp.	
7. exp Anatomy/ or Anatom*.mp.	
8. 1 or 2 or 3	
9. 4 or 5 or 6	
10. 7 and 8 and 9	
Total references from EMBASE + MEDLINE search imported in EndNote	2443
- MEDLINE	947
- EMBASE	1496
Duplicates removed in EndNote	- 494
Remaining studies imported in Rayyan.qcri	1949
Duplicates removed in Rayyan.qcri	- 241
Total of studies eligible for title and abstract screening	1708
Total duplicates removed	- 735

Supplementary table S2. Countries in the regional subgroups used for this analysis

Regional subgroup	Countries in regional subgroup
East Asia	Bhutan, Brunei, Cambodia, China, Indonesia, Japan, Laos, Malaysia, Mongolia, Myanmar, Nepal, North Korea, Philippines, Singapore, South Korea, Thailand, Timor-Leste, Vietnam
Europe, North America & Oceania	Australia, Austria, Belgium, Bulgaria, Canada, Czechia, Estonia, France, Germany, Hungary, Ireland, Latvia, Liechtenstein, Lithuania, Luxembourg, Monaco, Netherlands, New Zealand, Papua New Guinea, Poland, Romania, Slovakia, Slovenia, Switzerland, United Kingdom, United States of America
Southern Slavic countries, Russia & Central Asia	Afghanistan, Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Croatia, Georgia, Kazakhstan, Kyrgystan, Moldova, Montenegro, North Macedonia, Russia, Serbia, Tajikistan, Turkmenistan, Ukraine, Uzbekistan
Latin America & Caribbean	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
Mediterranean Basin	Andorra, Spain, Italy, Greece, Cyprus, Holy See, Malta, Portugal, San Marino
Middle East & North Africa	Algeria, Bahrain, Cabo Verde, Chad, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Mali, Mauritania, Morocco, Niger, Oman, Palestine State, Qatar, Saudi Arabia, South Sudan, Sudan, Syria, Tunisia, Turkey, United Arab Emirates, Yemen
Nordic countries	Denmark, Finland, Iceland, Sweden, Norway
South Asia	Bangladesh, India, Maldives, Pakistan, Sri Lanka
Sub-Saharan Africa	Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Comoros, Congo-Brazzaville, Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, Tanzania, Togo, Uganda, Zambia, Zimbabwe
Non-classified countries	Fiji, Kiribati, Marshall Islands, Micronesia, Nauru, Palau, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu

These regional subgroups are based on research by Rawshani et el. and Rotimi et al.[1, 2].

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Supplementary table S3. Included studies

Number	Reference
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Supplementary table S4. Pooled analyses of proportions of anatomical biliary variants (ABVs)

Type	Proportion (%)	95% CI (%)
Overall (n = 11706)		
1	65.9	64.8 – 67.1
2	14.2	13.1 – 15.4
3	11.7	10.9 – 12.5
4	6.5	6.0 – 6.9
Other	1.7	1.2 – 2.1
Studies including type 5 anatomy (n = 7226)		
1	64.6	63.0 – 66.2
2	15.4	13.8 – 17.1
3	12.1	11.1 – 13.2
4	6.6	6.1 – 7.2
5	0.6	0.4 – 0.8
Other	0.5	0.098 – 0.99
East Asia (n = 4808)		
1	69.6	68.1 – 71.1
2	10.8	9.9 – 11.8
3	12.0	10.7 – 13.3
4	6.3	5.5 – 7.2
Other	1.2	0.7 – 1.7
Europe, North America & Oceania (n = 221)		
1	59.3	52.9 – 65.7
2	17.6	11.3 – 24.1
3	12.7	6.3 – 19.1
4	10.0	2.6 – 16.4
Other	0.5	0 – 6.9
Mediterranean Basin (n = 273)		
1	64.9	0.597 – 0.707
2	14.3	0.092 – 0.201
3	12.8	0.077 – 0.187
4	6.6	0.015 – 0.124
Other	1.5	0 – 0.073
Middle East and North Africa (n = 5882)		
1	63.5	61.4 – 65.7
2	16.1	13.9 – 18.4
3	11.2	9.9 – 12.5
4	6.2	5.8 – 6.7
Other	2.8	1.9 – 3.8
South Asia (n = 522)		
1	56.9	52.7 – 61.2
2	21.8	17.6 – 26.2
3	9.6	5.4 – 13.9
4	5.6	1.3 – 9.9
Other	6.1	1.9 – 10.5

Supplementary table S5. Comparison of commonly used classification systems.

Our classification	Huang classification	Choi classification	Ohkubo classification	Couinaud classification
1	A1	1	A, D	A
2	A3	3A	C	C1, D1, D2
3	A2	2	B	B
4	A4	3B	E	C2
5	A5	3C	-	F
Other	-	4, 5A, 5B, 6	F, G	E1, E2

Supplementary figure 1. PRISMA Flow chart