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ORIGINAL ARTICLE

Epidemiology of Budd-Chiari syndrome: A systematic review and meta-analysis

Yingying Li[a,b], Valerio De Stefano[c], Hongyu Li[a,*], Kexing Zheng[a,b], Zhaohui Bai[a,d], Xiaozhong Guo[a], Xingshun Qi[a,*]

[a] *Department of Gastroenterology, Northern Theater Command General Hospital (formerly General Hospital of Shenyang Military Area), Shenyang, Liaoning Province 110840, PR China*
[b] *Post-graduate College, Jinzhou Medical University, Jinzhou 121001, PR China*
[c] *Servizio di Ematologia, Policlinico Agostino Gemelli, Largo Gemelli 8, 00168 Rome, Italy*
[d] *Post-graduate College, Shenyang Pharmaceutical University, Shenyang 110840, PR China*

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Budd-Chiari syndrome;
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Meta-analysis

Summary
Background and aims: The global epidemiological data of Budd-Chiari syndrome (BCS) are scant. A systemic review and meta-analysis aimed to estimate the incidence and prevalence of BCS.
Methods: PubMed, EMBASE, and Cochrane Library databases were searched. The Newcastle-Ottawa Scale was used to assess the study quality. The pooled incidence and prevalence of BCS with 95% confidence intervals (CIs) were calculated by using a random-effect model. The heterogeneity was assessed by the Cochran's *Q*-test and I^2 statistics. Subgroup analysis was conducted based on the study region (Asia or Europe).
Results: Overall, six studies were included. Among them, 2 studies were performed in Asian countries (i.e., Japan and South Korea) and 4 in European countries (i.e., Denmark, Sweden, Italy, and France). All of them were of high quality. The annual incidence of BCS was 0.168—4.09 per million. The prevalence of BCS was 2.40—33.10 per million. Meta-analyses showed that the pooled annual incidence of BCS was 1 per million (95% CI = 0.225—3 per million) and the pooled prevalence of BCS was 11 per million (95% CI = 4—21 per million). The heterogeneity among studies was statistically significant. Subgroup meta-analyses demonstrated that the pooled annual incidence of BCS was 0.469 per million in Asia and 2 per million in Europe and the pooled prevalence of BCS was 5 per million in Asia.
Conclusion: Evidence from meta-analyses of existing literature confirmed that BCS should be a rare vascular liver disease. BCS may not be more common in Asia than Europe. More epidemiological data in other countries should be warranted.

* Corresponding authors.
E-mail address: xingshunqi@126.com (X. Qi).

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Introduction

Budd-Chiari syndrome (BCS) is a vascular disease of the liver defined as hepatic venous outflow obstruction, usually located in the hepatic vein and inferior vena cava (IVC) [1], which can lead to acute liver failure, liver cirrhosis, and even hepatocellular carcinoma. If untreated in a timely fashion, BCS is potentially lethal. Primary BCS is often related to multiple thrombophilic conditions, including primary myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, inherited thrombophilia (i.e., deficiencies of natural anticoagulants and mutations of factor V Leiden and prothrombin G20210A), antiphospholipid antibodies, and circumstances at risk, such as pregnancy [2—5]. Secondary BCS is mainly related to tumor invasion and compression [6,7].

It is important for public health policy makers and professional physicians to understand the epidemiological distribution of a disease. However, the global epidemiological data about BCS are lacking at present. On the other hand, based on the large-scale single and multicenter studies from China [8,9] and Europe [10], it seems that the absolute number of cases with BCS is larger in Asia than West. However, some scattered studies from different regions reported inconsistent epidemiological data. In this setting, it is necessary to systematically identify the existing literature, to combine the published data regarding the incidence and prevalence of BCS, and to explore the epidemiology of BCS among regions.

Methods

Registration

The meta-analysis was registered in PROSPERO with a registration number of CRD42018102158.

Search strategy

All published literature regarding the epidemiology of BCS was searched via the PubMed, EMBASE, and Cochrane Library databases. The search items were ''Budd-Chiari syndrome'' AND ''epidemiology''. The last search was conducted on June 30, 2018.

Study selection

Inclusion criteria were as follows:

- the incidence and/or prevalence of BCS were reported;
- the epidemiology of BCS was explored in general population, but not specific population;
- the regions and countries were unrestricted.

Exclusion criteria were as follows:

- duplicates;
- case reports;
- letters, comments, and/or editorials;
- reviews and/or meta-analyses;
- irrelevant studies;;
- the data regarding study population cannot be extracted.

Definition

Definition of BCS was primarily based on the original studies included in the meta-analysis. Secondary BCS due to tumor invasion and compression or liver transplantation was not intentionally excluded.

Data extraction

The following data were extracted from the included studies: first author, publication year, country, data source, identification of cases, age of cases, target population, survey periods, study population, total case size, and incidence and/or prevalence of BCS.

Study quality

The quality of included studies was assessed by the Newcastle-Ottawa Scale. The following study characteristics were assessed:

- selection (Score 0—4);
- comparability (Score 0—2), and;
- outcome (Score 0—3).

The maximum Score is 9. A Score of 0—3, 4-6, and 7—9 represents low, moderate, and high quality, respectively.

Statistical analysis

The StatsDirect statistical software version 3.0.113.0 (StatsDirect Ltd, Sale, Cheshire, UK) was used to calculate the incidence and prevalence of BCS. The incidence and prevalence of BCS from each study was pooled to obtain a global incidence and/or prevalence with 95% confidence interval (95% CI). We performed meta-analyses by using a random-effect model. We used the Cochran's Q-test and I^2 statistics to assess the heterogeneity. $P < 0.1$ or $I^2 > 50\%$ was considered as a statistically significant heterogeneity. Subgroup analyses were conducted based on the study region (Asia or Europe). We did not assess the publication bias because only a small number of studies were included. A two-side $P < 0.05$ was considered as a statistical significance.

Results

Study selection

Overall, a total of 1325 papers were identified via the 3 databases, and another one paper was identified via manual search. Finally, 6 studies [11—16] were finally included in this systematic review and meta-analysis (Fig. 1). Notably, one study comprised of two cohorts [16].

Study characteristics

Characteristics of the included studies are demonstrated in Table 1. All included studies were published between 1991 and 2018. Among them, 4 studies were conducted in Europe

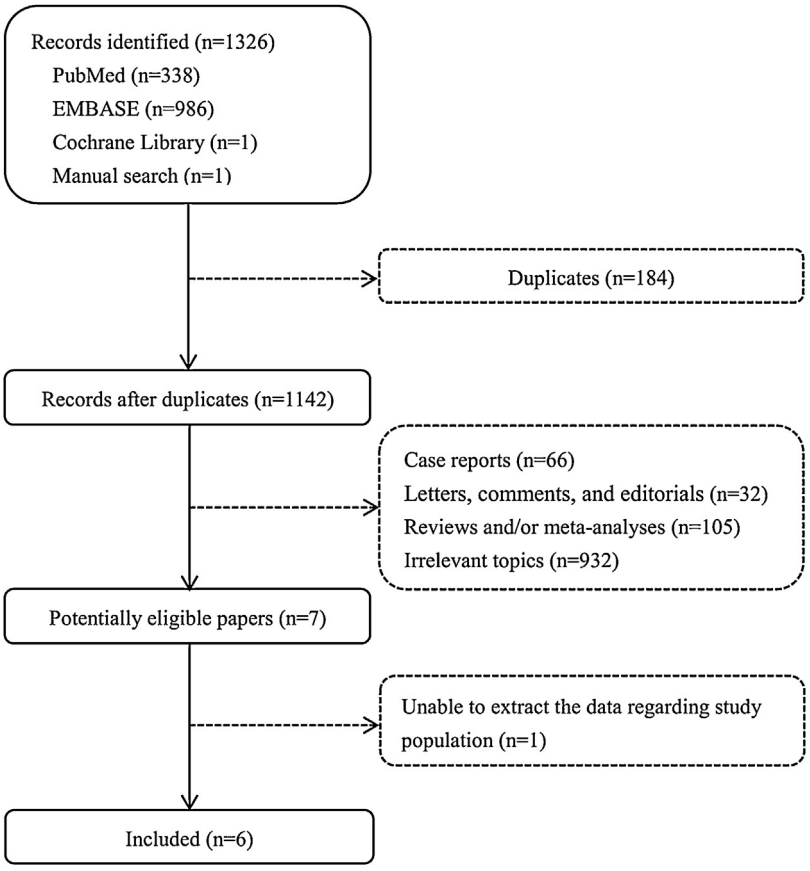

Figure 1 Flow chart of study selection.

and 2 in Asia (Appendix A, Supplementary Figure 1). Incidence of BCS was reported in 6 studies, and prevalence of BCS was reported in 4 studies.

Study quality

The Newcastle-Ottawa Scale score ranged from 7 to 9 points (Appendix A, Supplementary Table 1). All included studies were considered to be of high quality.

Incidence of BCS

Six studies reported the data regarding the annual incidence of BCS. Notably, there are two cohorts in the study by Ollivier-Hourmand et al., in which the 2010 cohort reported the incidence of primary BCS and the 2012 cohort reported the incidence of BCS and primary BCS. Finally, we selected the 2012 cohort data regarding the annual incidence of BCS, but not the 2010 or 2012 cohort data regarding the annual incidence of primary BCS, to maintain the similar eligibility criteria among these included studies.

The annual incidence of BCS was 1.68-40.9X10^{-7}. Among them, there was a statistically significant heterogeneity ($P < 0.0001$, $I^2 = 98.7\%$ [95% CI = 98.4—98.9%]). Using a random-effect model, the pooled annual incidence of BCS was 1X10^{-6} (95% CI = 2.25—30 $\times$ 10^{-7}) (Fig. 2).

Prevalence of BCS

Four studies reported the data regarding the prevalence of BCS. Because the 2010 cohort in the Ollivier-Hourmand's study reported the prevalence of primary BCS in inpatients or outpatients from 48 specialized liver units, it was attributed to specific population, but not general population. Thus, the data from the Ollivier-Hourmand's study were not finally included.

The prevalence of BCS was 2.40—33.10 $\times$ 10^{-6}. Among them, there was a statistically significant heterogeneity ($P < 0.0001$, $I^2 = 99.4\%$ [95% CI = 99.3—99.5%]). Using a random-effect model, the pooled prevalence of BCS was 11 $\times$ 10^{-6} (95% CI = 4—21 $\times$ 10^{-6}) (Fig. 2B).

Subgroup analyses

Incidence of BCS

Two studies reported the data regarding the annual incidence of BCS in Asia. Heterogeneity could not be calculated due to a small sample size. Using a random-effect model, the pooled annual incidence of BCS in Asia was 4.69 $\times$ 10^{-7} (95% CI = 0.22—10 $\times$ 10^{-7}) (Appendix A, Supplementary Figure 2A).

Four studies reported the data regarding the annual incidence of BCS in Europe. Among them, there was a statistically significant heterogeneity ($P < 0.0001$, $I^2 = 92.8\%$ [95% CI = 84.8—95.7%]). Using a random-effect model,

Table 1 Characteristics of the included studies.

First author (year)	Country	Source of cases	Identification of cases	Age of cases	Target population	Survey periods	Incidence/ prevalence	Study population (million)	Total case size (*n*)	BCS incidence/ prevalence
Almdal (1991)	Denmark	A computerized registry of all admissions to somatic hospitals in Denmark	WHO-CD	Unlimited	BCS	1981—1985	Incidence	5.1	13	0.5 per million per year
Okuda (1995)	Japan	Total 5625 units in Japan	NA	Unlimited	BCS	1989	Incidence	125	21	0.17 per million per year
							Prevalence	125	300	2.4 per million
Rajani (2009)	Sweden	All university hospitals and liver transplantation centers in Sweden	ICD-9/ ICD-10	Unlimited	BCS	1990—2001	Incidence	1.3	12	0.8 per million per year[a]
						1986—2003	Prevalence	1.3	43	1.4 per million[a]
Ki (2016)	Korea	Nationwide Health Insurance Review and Assessment Service claims database	ICD-10 I82.0	Unlimited	BCS	2011—2013	Incidence	49.99	137	0.87 per million per year[a]
						2009—2013	Prevalence	49.99	424	5.29 per million[a]
Ageno (2017)	Italy	Lombardy and piedmont regions in Northwestern Italy	ICD-9-CM 453.0	Unlimited	BCS	2002—2012	Incidence	13	287	2.1 per million
Ollivier-Hourmand(2018)	France	All 32 academic liver units and 16 large non-academic liver units in French	Standardized question-naire	≥ 18 years old	Primary BCS: BCS after liver transplantation, and those with malignancies except for MPN were excluded	2010	Incidence	44.07	30	0.68 per million per year
							Prevalence	44.07	178	4.04 per million
		Programme de médicalisation des systemes d'information	ICD-10 I82.0	≥ 18 years old	BCS	2012	Incidence	50.81	208	4.1 per million
					Primary BCS: BCS associated with ICD-10 codes of cancer, alcoholic and viral cirrhosis or liver transplantation were excluded	2012	Incidence	50.81	110	2.17 per million

BCS: Budd-Chiari syndrome; WHO-CD: world health organization classifications of diseases; ICD-9-CM: international classification of diseases, 9th, revision, clinical modification; MPN: myeloproliferative neoplasms.

[a] Age- and sex-adjusted rates.

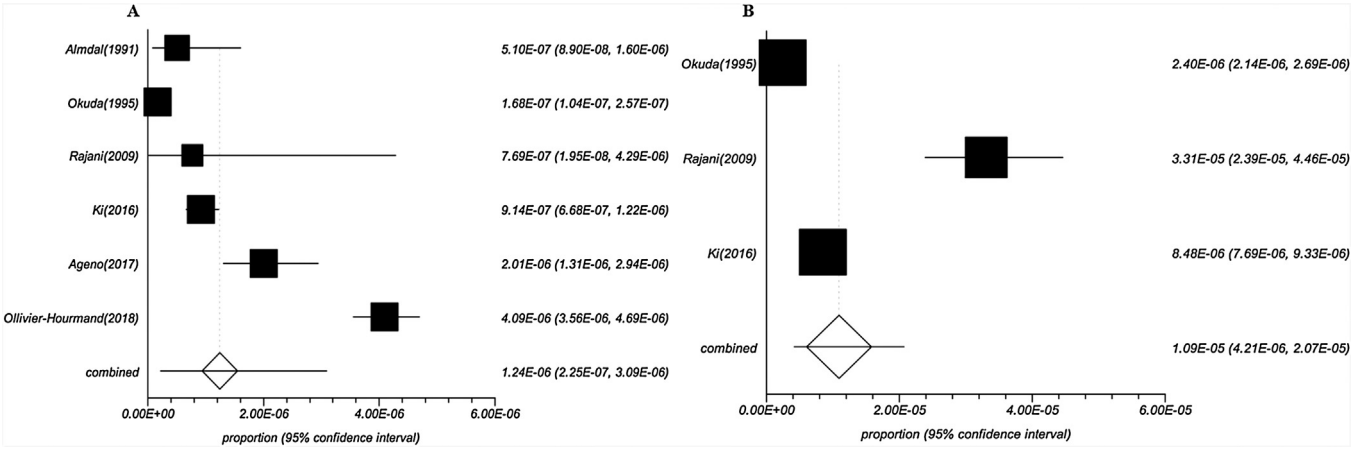

Figure 2 Forest plots showing annual incidence (panel A) and prevalence (panel B) of BCS.

the pooled annual incidence of BCS was 2×10^{-6} (95% CI = 5.98—40 $\times$ 10^{-7}) (Appendix A, Supplementary Figure 2B).

Prevalence of BCS

Two studies reported the data regarding the prevalence of BCS in Asia. Heterogeneity could not be calculated due to a small sample size. Using a random-effect model, the pooled prevalence of BCS in Asia was 5×10^{-6} (95% CI = 0.80—13 $\times$ 10^{-6}) (Appendix A, Supplementary Figure 3).

Two studies reported the data regarding the prevalence of BCS in Europe. However, Ollivier-Hourmand et al. reported the prevalence of primary BCS in inpatients or outpatients from 48 specialized liver units. Thus, only one European study was finally eligible, which reported that the prevalence of BCS was 1.4×10^{-6}.

Discussion

The epidemiology of major liver diseases in general population has been widely explored. The prevalence of hepatitis B virus was 1—5% in Europe [17]. The prevalence of hepatitis C virus was 0.2—2.4% among the 17 countries and regions all around the world [18]. The prevalence of non-alcoholic fatty liver disease was about 23.71% in Europe [19]. The annual incidence of drug included liver disease was 191 per million in Iceland [20]. The annual incidence of primary sclerosing cholangitis and primary biliary cirrhosis around the world was 0—13 per million inhabitants and 3.3—58 per million inhabitants, respectively [21]; and the prevalence was 0—162 per million inhabitants and 19.1—402 per million inhabitants, respectively. As compared to these above-mentioned liver diseases, BCS should be an extremely rare liver disease.

A previous systematic review regarding the epidemiology of BCS in China was conducted by Zhang et al. based on the Chinese-language literature in 2014 [22]. They reported that the incidence and prevalence of BCS in China would be 0.88 per million per year and 7.69 per million at a conservative estimation, respectively. However, the limitation of their systematic review was remarkable. First, they reviewed the medical history of BCS reported in the literature and then estimated the epidemiological data by a sum of cases reported. The data regarding the incidence and prevalence might be inaccurate. Second, the publication language of studies included in their systematic review was restricted. Only Chinese-language articles were included, but English-language articles were not considered. Third, the bias due to cases of misdiagnosis and missed diagnosis could not be neglected.

We found that the heterogeneity among the included studies was significant. The reasons should be analyzed. First, the included studies were conducted in different regions. Thus, the nature of general population was heterogeneous and the environmental exposure and gene susceptibility were also variable [2,23,24]. Hepatic vein thrombosis is the most common type of primary BCS and myeloproliferative neoplasms are a major risk factor of primary BCS in Western countries. By comparison, membranous obstruction of the IVC is more common and myeloproliferative disorders are rare in Asia countries [25]. Second, the diagnostic criteria or methods of survey were different among the included studies. Questionnaire was used in Okuda's study and Ollivier-Hourmand's study [12,16]. Case identification by the World Health Organization Classifications of Diseases or International Classification of Diseases was used in other studies [11,13—15]. In addition, the methods of survey were also different between the two cohorts of the Ollivier-Hourmand's study. The 2010 cohort was based on a standardized questionnaire from the specific liver units; by comparison, the 2012 cohort was based on the International Classification of Diseases-10 code from the database of hospital nationwide discharge diagnosis. Generally, these heterogeneous criteria and methods had different degrees of sensitivity for inclusion of incidental cases. Third, the characteristics of target population, such as type of BCS, were different. For example, the studies by Ageno [15] and Okuda [12] suggested that a proportion of BCS was secondary to malignancy, such as gastrointestinal cancer and hepatocellular carcinoma. Fourth, the incidence and prevalence of BCS were much higher in the studies by Ageno [15] and Rajani [13], respectively. On the other hand, the incidence reported by Rajani et al. [13] was quite lower than that reported by Ageno et al. [15]. This difference might be attributed to the heterogeneous enrollment period among studies [26]. With the improvement of imaging tech-

niques, the diagnosis of thrombosis within abdominal vessels became easier. In a nationwide population-based study from Denmark, a total of 1915 patients with splanchnic vein thrombosis were identified from 1994 to 2013. Of them, 14.1% were identified from 1994 to 1999, 23.2% from 2000 to 2005, and 62.7% from 2006 to 2013 [27]. Therefore, we believed that any estimate in the epidemiology of BCS should be time-framed [26]. Indeed, the Ageno's study recruited patients during the recent years (2002—2012) [15], so BCS could be more frequently observed.

The meta-analysis has the following major limitations. First, only a few studies on the epidemiology of BCS worldwide were performed. Second, subgroup analyses according to the gender, type of hepatic venous outflow obstruction, and major risk factors for BCS were unavailable because the relevant data could not be extracted. Third, the included studies were conducted in Europe and Asia, rather than America and Africa. Further studies should be warranted to explore the epidemiology of BCS from other regions.

In conclusion, based on the results of a meta-analysis, the incidence and prevalence of BCS were estimated as 1 per million per year and 11 per million, respectively. The incidence of BCS seemed to be a bit lower in 2 Asian countries (i.e., Japan and South Korea) than 4 European countries (i.e., Denmark, Sweden, Italy, and France). The unexpected findings should be cautiously interpreted, because the epidemiological data of BCS in China and India, which might have a larger number of BCS patients, were lacking and the heterogeneity of study design was remarkable among the included studies. Additionally, because most of epidemiological data were obtained when secondary BCS was not excluded, the actual epidemiological data regarding primary BCS should be further explored.

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Authors' contributions

Yingying Li: reviewed and searched the literature, wrote the protocol, collected the data, performed the statistical analysis and quality assessment, interpreted the data, and drafted the manuscript.

Valerio De Stefano: gave critical comments and revised the manuscript.

Hongyu Li and Xiaozhong Guo: checked the data and gave critical comments.

Kexin Zheng and Zhaohui Bai: searched the literature, wrote the protocol, collected the data, and performed the statistical analysis and quality assessment.

Xingshun Qi: conceived the work, reviewed and searched the literature, wrote the protocol, performed the statistical analysis, interpreted the data, and revised the manuscript.

All authors have made an intellectual contribution to the manuscript and approved the submission.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.clinre.2018.10.014.

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