REVIEW PAPER

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An overview of cord blood stem cell transplantation in Hong Kong

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ABSTRACT

Haematopoietic stem cell graft derived from cord blood is standard therapy for several haematological malignancies and other diseases. The study reports cases of public and private (family) cord blood biobanking services and the related hematopoietic stem cell transplantation ever performed in Hong Kong. The published original research papers and review articles from inception to Nov 2022 have been searched for on Pubmed, Microsoft Academic Search, and Google Scholar to identify reports on existing or terminated cord blood biobanking and transplantation service in Hong Kong. Moreover, all data publicly available on the official websites of the local cord blood banks and local mainstream media has been analysed. The public Hong Kong Red Cross Blood Transfusion Service delivers the highest quantity of haematopoietic stem cell transplants. Among the private sector, HealthBaby releases the most cord blood units for clinical use in diseases in both autologous and allogeneic administration, followed by Cordlife HK. Both public and private (family) cord blood biobanks have been and continue to contribute to the Hong Kong cord blood donor registry. However, the growth of the cord blood inventory is detrimental to donor-recipient matching for lifesaving therapy.

Introduction

In France in 1989, a 5-year-old boy with Fanconi anaemia received the first cord blood transplant (CBT) using a human leukocyte antigen (HLA)-matched sibling donor [1]. Since then, CBT has developed as a standard treatment or an accepted therapeutic modality for >100 haematologic, immunologic, neurologic, and metabolic diseases worldwide [2, 3]. Haematopoietic stem cell transplantation (HSCT) is the only option for curing numerous diseases, including Glanzmann's thrombasthenia, [4] relapsed B-cell acute lymphoblastic leukaemia [5], and sickle cell disease [6]. Worldwide, over 1.5 million HSCTs have been performed [7].

Cord blood represents a valuable source of HSC in addition to bone marrow (BM) and

peripheral blood (PB). Autologous or allogeneic transplantation with HLA-matched siblings, unrelated donors, and haploidentical donors has been performed on paediatric and adult patients for decades [8]. Cord blood transplant (CBT) has been widely used due to the high tolerance of HLA disparity accompanied by a low incidence of graft-versus-host disease, ease of collection, low risk of viral transmission, advancement of *in vitro* cord blood stem cell expansion and *in vivo* homing capacity, and growth of public or private (family) cord blood banks (CBB) worldwide [9, 10].

It was estimated to have over 450 CBBs worldwide; only half carry out in-house processing and storage, with the remaining outsourced to third-party facilities [11]. According to the World Marrow Donor Association, despite over 8 million cord blood units ready for transplant in public CBBs, 10,000–15,000 patients per year fail to identify a matched donor for CBT, especially for racial and ethnic minorities [12, 13]. As a result, CBBs of nation, public, and family have been calling for cord blood banking and donation to extend the inventory size for research and treatment.

Several international accrediting bodies have proposed specific, strong, and up-to-date guidelines or standards for auditing public and private (family) CBBs to ensure compliance with specified operations requirements from cord blood collection to clinical administration. These include the Foundation for the Accreditation of Cellular Therapy (FACT), the Association for the Advancement of Blood & Biotherapies, previously known as the American Association of Blood Banks (AABB), and the College of American Pathologists (CAP). FACT accreditation is the most widely-recognized and comprehensive CBB accreditation. It has been referred to as the evidence-based, objective criteria to evaluate the performance of both public and private (family) CBBs [14, 15]. The NetCord-FACT standard is the cornerstone of the FACT accreditation program for cord blood banking, as the only set of requirements to audit the clinical arm of cellular therapeutic products. As of 27 June 2022, 56 NetCord-FACT accredited CBBs have represented 23 countries on 5 continents. The NetCord-FACT standard applies to the procedures in a CBB covering cord blood donor management (for example, donor eligibility assessment) and collection, processing, testing (for example, maternal and neonatal blood and the final cryopreserved $CD34^+$-enriched cell products for HSCT), cryopreservation, storage, listing in CBB registry, search, selection, reservation, release, distribution, donor and patient informed consent or authorization and clinical administration of cord blood units (CBU) [16, 17].

The College of American Pathologists (CAP) provides an international laboratory accreditation and proficiency testing program for a broad spectrum of laboratory testing on human specimens and a biorepository to ensure testing accuracy and foster continuous modification [18]. CAP is a widely acknowledged leader in laboratory quality assurance. It accredits a suite of laboratory tests related to cord blood and stem cell processing, involving enumeration and viability of $CD34^+$ stem cells and (mono) nucleated cells in the blood or related products, blood group, and HLA typing, infectious disease serology of maternal blood, and sterility.

In this study, we overview the cord blood banking industry in Hong Kong. We summarise the active and inactive public and private (family) CBBs, reporting the relevant accreditation status of individual CBBs, the total number of CB-HSCT ever performed, types of HSCT, and the variety of treated diseases. This study would contribute to understanding the ecosystem of the local cord blood banking sector and promote public awareness of the clinical significance of cord blood banking and the relevant accreditations to CBBs for demonstrating compliance with international standards.

Material and methods

The overview of the cord blood industry in Hong Kong was conducted by referencing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. The PRISMA statement was presented in PRISMA 2009 Flow Diagram (**Supplementary Figure 1**).

Search Method

A comprehensive search covering published original research and review articles from inception to Nov 2022 on Pubmed, Microsoft Academic Search, WiseNews, and Google Scholar was per-

formed to identify reports on active and inactive cord blood biobanking and transplantation service in Hong Kong. The keywords combinations included "haematopoietic stem cells," "American Association of Blood Banks," "Association for the Advancement of Blood & Biotherapies," "Foundation for the Accreditation of Cellular Therapy," "College of American Pathologists," "cord blood bank," "unrelated haematopoietic stem cell transplant," "stem cell transplantation," "cord blood stem cell transplantation." Moreover, all information publicly available on the official websites and annual reports of the local cord blood banks and local mainstream media have been analysed. Reference lists of identified articles were searched for additional references. The search was not restricted to any languages or publication types. Statistical analyses and graphical representation were performed using GraphPad Prism 9.3.1 (GraphPad Software, USA).

Eligibility criteria and study selection

Publications that meet the following criteria were included for analysis: (I) Peer-reviewed review, research article, or case study referring to the cord blood biobanking industry or the direct cord blood transplant in Hong Kong or oversea institutes involving locally banked cord blood units; (II) Subject: human with any indications such as Thalassaemia, hypoxic-ischemic encephalopathy, anaemia, cerebral palsy and neuroblastoma. Duplicated records were removed during the screening stage. Publications were excluded if the full-text or key data were inaccessible. A thorough literature search of the selected full-text publications was performed to determine their eligibility. All retrieved eligible publications were included and imported into EndNote 20.3 (Bld 16073) for downstream descriptive and quantitative analyses.

Results

Overview of HSCT cases released by local public and private (family) CBBs

Hong Kong has two public and seven private (family) CBBs. The first and the most extensive public CBB was established by the Hong Kong Red Cross Blood Transfusion Service (BTS) managed by the Hospital Authority, a statutory body established on 1 December 1990 under the Hospital Authority Ordinance to manage all public hospitals in Hong Kong, introduced in utilization for processing, storage, and releasing CBU for HSCT in 1998. The CBB was renamed "The Hong Kong Red Cross Catherine Chow Cord Blood Bank" in 2007. The BTS-CBB received the NetCord-FACT accreditation in April 2013 and also became the first FACT-accredited CBB in Hong Kong. The number and other relevant clinical information on HSCT contributed by BTS is generally incomplete and non-disclosable; the data reported is primarily retrieved from the annual reports from 2015 to 2021 and peer-reviewed literature. Fifty-four HSCT cases were performed by the transplant centres using CBUs from BTS using donated cord blood collected from local public hospitals from 2015 to 2021, as the annual reports indicate. An additional 9 unrelated CBTs were delivered from 1999 to 2003, [20] with a total of 63 HSCTs confirmed (**Figure 1**). The CBT data between 2004 and 2014 are private.

Given that the mean value of HSCT within the reported years is 9, we reasonably estimated the HSCT performed in the missing period from 2004 to 2015 to be 99, adding to the cumulative HSCT cases using the CBU processed by BTS reaching 162. Mononuclear Therapeutics (MonoTx™) is a private facility receiving donations of CBU from the public Prince of Wales Hospital affiliated with the Chinese University of Hong Kong. It is intended for related and unrelated transplantation, where the donor is eligible to request autologous or related transplantation if the donated CBU is not yet released, which, however, has not been reported by MonoTx™.

Among the seven private (family) CBBs, Healthbaby delivered the highest number, with five processed CBUs for transplantation so far, followed by Cordlife HK (three cases) and Cryolife (one case). While BioCell, Smart Cells, ProStemCell, and Athena Life have not released any CBUs for HSCT. BioCell ceased the cord tissue and blood banking service in 2020, with the cryopreserved cord tissue and CBUs relocated to other private (family) CBBs for storage [21]. Smart Cells ships the collected cord blood samples overseas for further processing and storage. The local cord blood banking services of the other two private (family) CBBs (i.e., ProStemCell, and Athena Life) are either terminated or inactive.

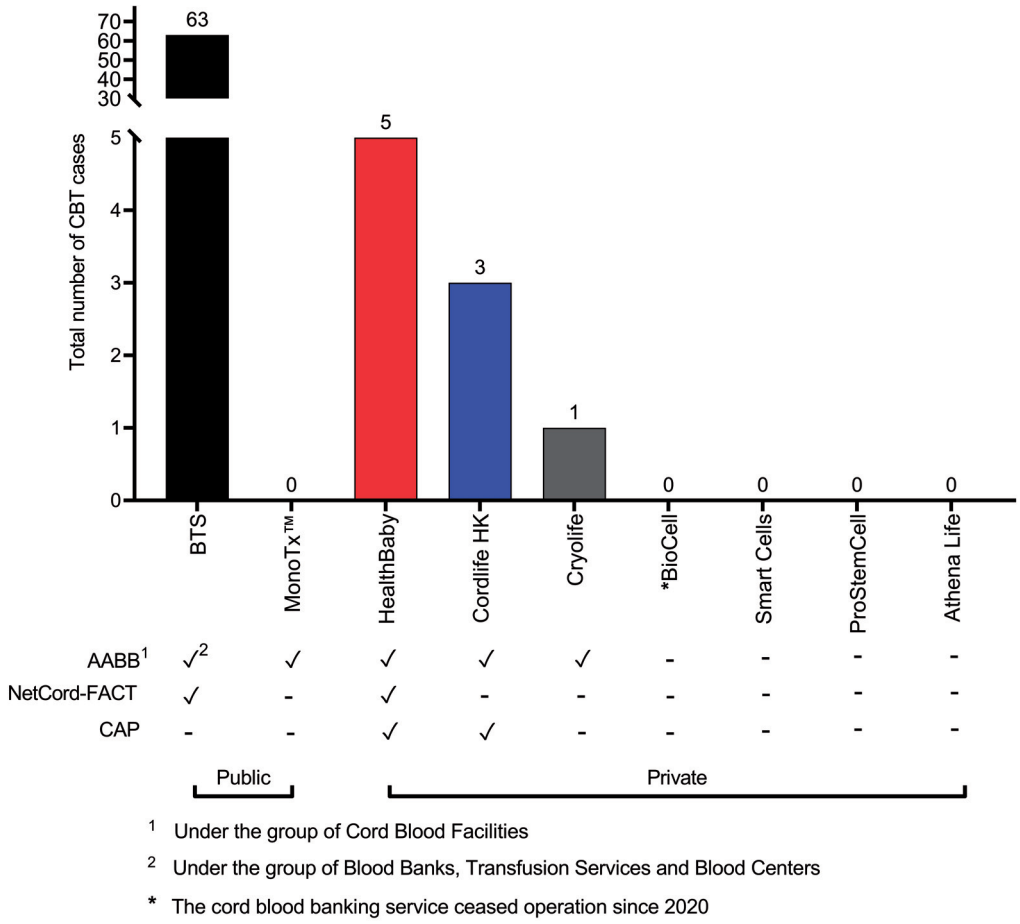

Figure 1. The number of cord blood transplant (CBT) cases of the public and private (family) cord blood banks (CBBs) and their respective accreditation status

Accreditation status awarded to CBBs

As shown in **Figure 1**, all five active public and private (family) CBBs (i.e., BTS, MonoTx™, HealthBaby, Cordlife HK, and Cryolife) are accredited by AABB. Notably, BTS is not accredited under the category of Cord Blood Facilities like the others but under the Blood Banks, Transfusion Services, and Blood Centres. The Hong Kong Red Cross Catherine Chow Cord Blood Bank, operated by BTS, is the first local CBB accredited by NetCord-FACT in March 2013, highlighting its landmark achievement in CBB provided for clinical use in the HK cord blood industry. HealthBaby is the first and only private (family) CBB accredited by the NetCord-FACT accreditation since March 2018.

Despite CAP accreditation absence, numerous medical testing services supported by the reference testing laboratories operated by BTS have been accredited by the Hong Kong Laboratory Accreditation Scheme (HOKLAS) with the ISO 15189:2012 "Medical laboratories – Requirements for quality and competence" (Registration No. HOKLAS 816P) followed. In categories of Clinical Microbiology and Infection, Haematology, and Medical Genetics (Molecular Genetics), they involved ABO and Rh(D) typing, haematology counting, viable CD34+, and nucleated cell enumeration, serology, bacterial surveillance tests, Nucleic Acid Amplification Test of Hepatitis B and C virus, and human immunodeficiency virus (HIV).

FACT-accredited HealthBaby and Cordlife HK are the only private (family) CBBs fully accredited under the laboratory accreditation scheme of CAP. The testing performed there is relevant to cord blood banking, covering blood group typing, serology test of maternal blood, and completed cell count with differential, viability and enumeration of CD34+ and mono(nucleated) cells in the pre-processed or processed cord blood. They also provide antimicrobial testing of the final cryopreserved cord blood products. It is worth noting that the satisfaction with the proficiency

testing (PT) requirement by CAP or other external quality assurance programs fails to represent the accreditation corresponded (Please see the Discussion for further details). In addition, HealthBaby is the only CBB in Hong Kong accredited by all three international professional bodies for cord blood banking.

Indications and transplant types of CBT

Li et al. reported that eight patients received CBTs from unrelated donors using the cord blood processed by FACT-accredited BTS (five with leukaemia, one with non-Hodgkin's lymphoma, and one with X-linked adrenoleukodystrophy) from 1999 to 2003 [20]. Other than that, the diseases and the types of transplants treated by BTS-stored cord blood were non-disclosable.

We focused on the indications and the infusion types of CBT adopting the CBUs processed by private (family) CBBs. As **Figure 2** shows, the nine transplant cases refer to non-haematologic disorders (cerebral palsy, neuroblastoma, and hypoxic-ischemic encephalopathy (HIE)) and haematologic diseases (thalassemia major and Fanconi anaemia). HealthBaby delivered the most CBUs for nearly all indications except HIE and served as the only facility to provide CBUs for Fanconi anaemia in 2014. HealthBaby and Cordlife HK delivered CBUs for thalassemia major, neuroblastoma, and HIE, where the latter is

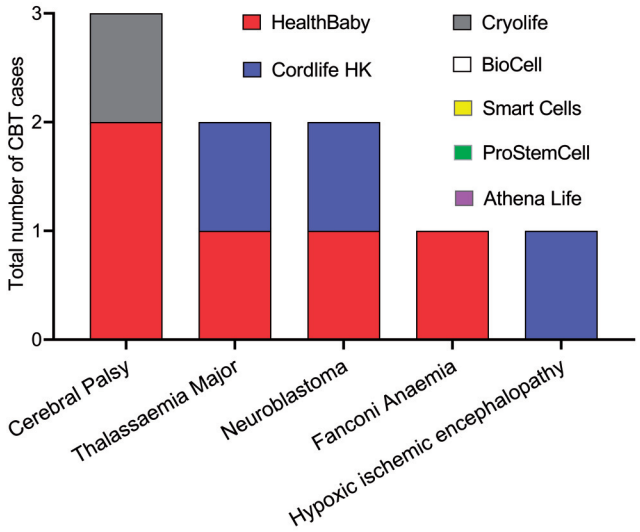

Figure 2. The number of cord blood transplant (CBT) cases for different indications using the cord blood units processed by the private (family) cord blood banks

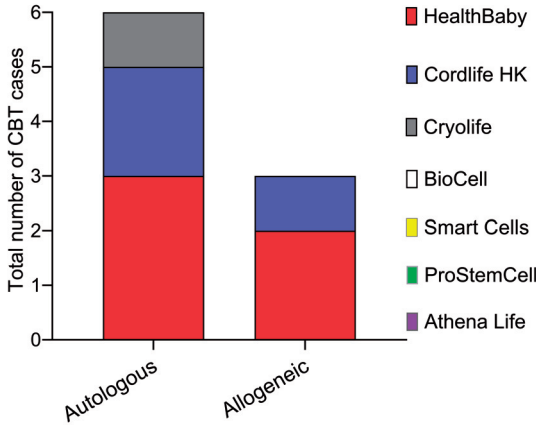

Figure 3. The number of autologous and allogeneic cord blood transplant (CBT) cases using the cord blood units processed by the private (family) cord blood banks

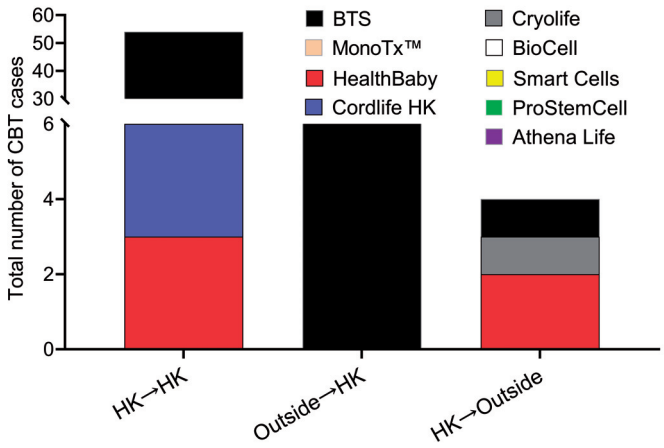

Figure 4. The number of cord blood transplant (CBT) cases using the cord blood units processed and released by the public and private (family) cord blood banks for local administration (HK→HK) or oversea administration (HKRegularOutside), or using the cord blood imported from an oversea facility for local administration

the only facility releasing CBUs for HIE in 2022. In addition, Cryolife released a CBU for cerebral palsy along with the two additional by HealthBaby.

According to **Figure 3**, both facilities released CBUs for autologous and allogeneic (related) use. Moreover, Cryolife delivered an autologous transplant for its single-release case.

Most transplants using the CBUs are performed in Hong Kong's public hospitals. **Figure 4** highlights that BTS released the most CBUs for HK→HK transplantation, with the number 48, followed by HealthBaby (three cases) and Cordlife HK (three cases). BTS is the only facility receiving CBUs from oversea facilities to provide for the six local transplantations (OutsidRegularHK). HealthBaby released three in-house processed CBUs for two oversea CBTs (HK→Outside) in the Duke University Hospital, Durham, North Carolina), and a single CBT delivered by BTS and Cryolife.

Discussion

In this study, we carried out an overview of the public and private (family) cord blood sectors in Hong Kong. We reported that the FACT-and HOKLAS-accredited public BTS released the most significant number of CBUs for allogeneic administration. HealthBaby, accredited by NetCord-FACT, AABB, and CAP, released the highest number of CBUs for autologous and allogeneic use for neurologic and hematologic disorders in private (family) CBBs. Along with the Divison of Transplantation and Immunogenetics of the public Queen Mary Hospital (CAP-accredited No.: #7175525), HealthBaby and Cordlife HK are the only CBBs in Hong Kong to offer CAP-accredited tests for cord blood testing, as are accredited by CAP, which offers the most considerable PT or external quality assessment program fulfilling the requirements of ISO/IEC 17043:2010 in the field of the PT provider (general laboratory, clinical, biochemical genetics, and anatomic pathology) granted by the leading accrediting body ANSI National Accreditation Board. Participating in the CAP PT program facilitates the evaluation of clinical laboratory performance and contributes to demonstrating a commitment to continuous modifications [22].

It must be explicitly stressed that conducting the CAP PT programme is only one of the quantities of requirements to attain full accreditation. It is accompanied by other stringent requirements not covered in the CAP PT programme and involves a quality management program, laboratory information system, competency assessment program, and document control system. All the programmes and systems are pivotal to monitoring the laboratory's performance and delivering accurate testing results. Moreover, a facility accredited by CAP does not mean that all performed tests are CAP-accredited, while only a selected panel of conducted tests is accredited. Therefore, expectant parents are highly recom-

mended to confirm and acknowledge whether the testing per se is accredited by CAP rather than the facility.

FACT-accredited BTS has continued to provide high-quality CBUs for unrelated transplants. Both AABB and FACT guide autologous and allogeneic administration. According to the AABB Standards for Cellular Therapy Services (10th Edition), effective on 1 July 2021, several reference standards apply to the autologous and allogeneic use, such as 5.12A, General Requirements for Cellular Therapy Product Donors; Reference Standard 5.12B, Clinical Evaluation and Laboratory Testing of Living Allogeneic Donors; Reference Standard 5.12C, Clinical Evaluation and Laboratory Testing of Autologous Donors; Reference Standard 5.12D, Clinical Evaluation and Laboratory Testing of Mothers of Cord Blood or Gestational Materials Donors; and Reference Standard 5.12E, Clinical Evaluation and Laboratory Testing of Cadaveric Donors. These standards are descriptive, and the facility determines the implementation of the related policy, process, and procedure, resulting in variations of standards from site to site.

On the other note, the NetCord-FACT's Cord Blood Accreditation Manual (the latest edition is the seventh) gives broader, detailed, and more specific requirements covering cord blood collection, processing, testing, cryopreservation, and storage, release, distribution, listing, and clinical administration. Distinguished from AABB, NetCord-FACT formulates detailed specification requirements pointing to CBUs for unrelated and related clinical administration in terms of the viability and cell count of both nucleated cells and $CD34^+$ cells before and after cryopreservation (before release to the clinical program), HLA typing, potency test (for example, colony-forming unit), microbial screen, donor screening and testing, identity verification, labelling, accompanying documents at distribution. The corresponding explanation and example of each reference standard are provided for facilitating the establishment, implementation, and maintenance of the quality management system. In Hong Kong, only the public BTS and private (family) HealthBaby CBBs acquired accreditation from NetCord-FACT. There is no specific ordinance regulating cord blood storage in Hong Kong. However, the collection and use of cord blood are subject to regulatory control of existing ordinances under different circumstances. The local regulatory authority recommended that FACT and AABB accreditations provide a third-party audit related to the relevant processes in CBBs and cell therapy (https://www.advancedtherapyinfo.gov.hk).

Compared to bone marrow, cord blood is profoundly characterised by a viable source of stem cells. The collection is non-invasive, accompanied by the more relaxed HLA matching requirement, expediting the course of transplantation, especially for ethnic and racial minorities. Nonetheless, the $CD34^+$ cell count (i.e., cell dose) is limited per CBU, and the consideration of the patient's weight and HLA profiles for matching is required for clinical administration; thus, CBU is primarily adopted in paediatric patients [23, 24]. Plenty of clinical studies have supported the safety and clinical efficacy of double partially- HLA-matched CBUs graft, overcoming the inadequately dosed single-unit CBT [25]. The advanced *in vitro* cord blood stem cell expansion development has recently fueled clinical transplantation [26, 27] Due to the insufficient availability of public clinical data on the CBT and HLA genotype and haplotype frequencies, it is intractable to determine the HLA-match likelihoods for CBT. Multi-national studies over the two decades indicated that, in the USA, UK, India, Japan, and South Korea, the probability of locating a (4/6) HLA-match CBU for transplant is nearly 100% when the inventory size reaches 100,000 CBUs [28, 29]. The likelihood of identifying a 5/6 HLA-matched unit for graft reaches over 98% in India, Japan, and South Korea [29]. A recent report released by the Institution of Guangdong Cord Blood Bank and Guangdong Women and Children Hospital indicated that 99% of patients could find a 4/6 HLA-matched CBUs for transplantation [30].

In China, the rapid growth of disease- and population-based biobanks since the late 1990s has driven scientific research and personalised medicine [31]. However, problems and challenges arising from the fast development of biobanks include the need for more implementation and enforcement of policies and laws related to sample collection and management, informed consent procedures, confidentiality, and ethical review. In addition, the policy, process, and procedures for specimen collection, logistics management, processing, storage, data management, and listing have yet to unified. Furthermore, unstable fund-

ing support for biobanks and inadequate public education campaigns, public involvement, and engagement strategies discourage sustainable development for Chinese biobanks [31–36].

In contrast, the Japanese government established the Japan Agency for Medical Research and Development (AMED) to consolidate national resources and reconstruct the funding mechanisms and management system under an initiative named National BioResource Project, to enhance the quality management of biobanks and information sharing across nations [36]. Japan's revitalization strategy and master plan development of biobanking led by AMED include the development of an open-access National Centre Biobank Network's Electronic-Catalogue-based Database for data sharing among communities for collaboration [37]. The Database provides a breadth of high-quality and up-to-date clinical data, including detailed patient's medical history, life history, disease information, and biological sample information to promote medical research and development [37]. A centralised regulatory agency is crucial to establish and enforce rules on operation, management, and information sharing among biobanks, promoting public awareness and facilitating community engagement in biobanking.

Barini et al. reported the effects of the time interval from the sample collection in a medical centre to its processing in a CBB on the CBU's quality [38]. The study found that the mean and median of the total number of nucleated cells, viable cells, and $CD34^+$ cells were significantly reduced if the time between collection and processing was within 24 hr compared to 48 hr and 72 hr. Smart Cells delivers the cord blood sample to an oversea processing facility, which inevitably lengthens the turnaround time for the processing. As a result, the quality of the cryopreserved CBU may be compromised. A customer should be fully informed about the extended transport effects on the quality of the CBU.

Prior studies highlighted that the utilization rates (i.e., the ratio of transplanted to banked CBUs) in public and family CBBs are 3–4% and 0.04–0.0005%, respectively [39]. However, the local cord blood inventory information is not publicly accessible, and the utilisation rate in Hong Kong is unclear. On a related note, a recent survey report released by the Asia-Pacific Blood and Marrow Transplantation Group provided an overview of the transplant rate (i.e., the number of CBT per 10 million residents) in 20 countries or regions, including Hong Kong in the Asia-Pacific region [40]. The report indicated that the transplant rate in Hong Kong is 1.4, the same as China, which is lower than other developed countries such as Japan (105.3%), Singapore (16.1%), and Australia. (11.2%), Korea (8.9%), and New Zealand (6.4%) [40]. Numerous cost-effective strategies have been proposed to increase therapeutic value to patients with the maximal economic sustainability of CBBs [41]. A study based on the data from the National Marrow Donor Program administered by the Health Resources and Service Administration in the USA found that the annual societal benefit, based on the estimated increment of life expectancy after CBT, is between USD 5 million and 1.5 billion. The amount is over an order of magnitude compared to the annual operational cost of running cord blood banks of USD 60–70 million [42]. Considering that more diseases are treatable by CBT and a relatively low probability for specific racial and ethnic minorities to obtain a match from other HSC sources, it is justifiable to allocate additional government sources to support the local cord blood system and infrastructure [42].

As shown in celltrials.org, the percentage of births banking cord blood in Hong Kong is 3.5%, referring to the number of units banked in the most recent year with data divided by the number of births in the same year out of the 57 examined territories. It is higher than in other developed countries such as the USA/Poland/Spain (3%), Australia (1.4%), the UK (0.3%), Japan (0.8%), Germany (0.7%), and France (0.08%). Still, it is lower than nearby territories such as Singapore (30%), Taiwan (7%) and South Korea (6.8%) (**Supplementary Table 1**). A collaborative study by the Chinese University of Hong Kong and the public Queen Elizabeth Hospital indicated that 78.2% of pregnant women are unaware of the availability of private (family) CBBs in Hong Kong. Only 20.3% of expectant women knew BTS might offer HSCT in case of medical requirements. Nearly 90% of expectant mothers agreed that the HK government should allocate more resources to cord blood banking and promote public education on the subject matter [43]. Besides, patients, transplant physicians, and the cord blood industry are encouraged to publicly provide data about the clinical outcome of

CBT to increase transparency and enable patients to make informed choices about their healthcare. The government, clinicians, and the community should work together to elevate social awareness of the clinical relevance of cord blood banking in both public and private (family) CBBs, as a crux element of antenatal care.

Numerous factors contribute to the low public awareness and willingness to cord blood banking and low utilization rates, such as employment status, educational level, uncertainty over the legitimate use of cord blood stem cell transplant, poor regulatory oversight of cord blood banking operation, cost of banking, and concern on safety and cell recovery after cryopreservation for clinical application. Therefore, it is pivotal for a government to mobilise resources to set up a regulatory body to oversee the legislation, policies, and standards implementation. These are necessary to regulate the cord blood banking business and launch education campaigns to promote the socio-economic benefits of biobanking to the general public and clinicians. In addition, it is also vital to reorganise funding mechanisms to address the economic vulnerability biobanks face to sustain the cord blood industry [44–48].

There are several limitations of this study. First, the CBT data from 2004 to 2014 delivered by BTS-CBB needed to be disclosable, and the number of HSCTs using the CBU processed by BTS was estimated. Some of the CBT information provided by other private or family CBBs may not be updated, leading to the potential under- or over-estimation of HSCT facilitated by local CBBs. Besides, a minimal amount of clinical data on individual CBT was released, impeding us from conducting a comprehensive analysis of the dosing, safety, and clinical efficacy of cord blood stem cell transplantation.

Conclusions

Public and private CBBs are the driving factor in enhancing the local inventory for potential autologous and allogeneic (related and unrelated) applications. Therefore, dedicated efforts to expand the inventory size and promote public awareness of the clinical significance of cord blood banking are crucial to nurturing the cord blood industry in Hong Kong.

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Drafting of the manuscript: Leung CK.
Critical revision of the manuscript for important intellectual content: Leung CK.

Leung CK had full access to the data, contributed to the study, approved the final version for publication, and took responsibility for its accuracy and integrity.

Abbreviations
HSCT: Hematopoietic stem cells transplantation; BM: Bone marrow; CBB: Cord blood bank; CBT: Cord blood transplant; CBU: Cord blood unit; PB: Peripheral blood; HLA: Human leukocyte antigens; AABB: Association for the Advancement of Blood & Biotherapies formerly known as American Association of Blood Banks; FACT: Foundation for the Accreditation of Cellular Therapy; CAP: College of American Pathologists; PT: Proficiency testing.

Conflict of interest statement
The authors declare no conflict of interest.

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Ethics approval
Not applicable.

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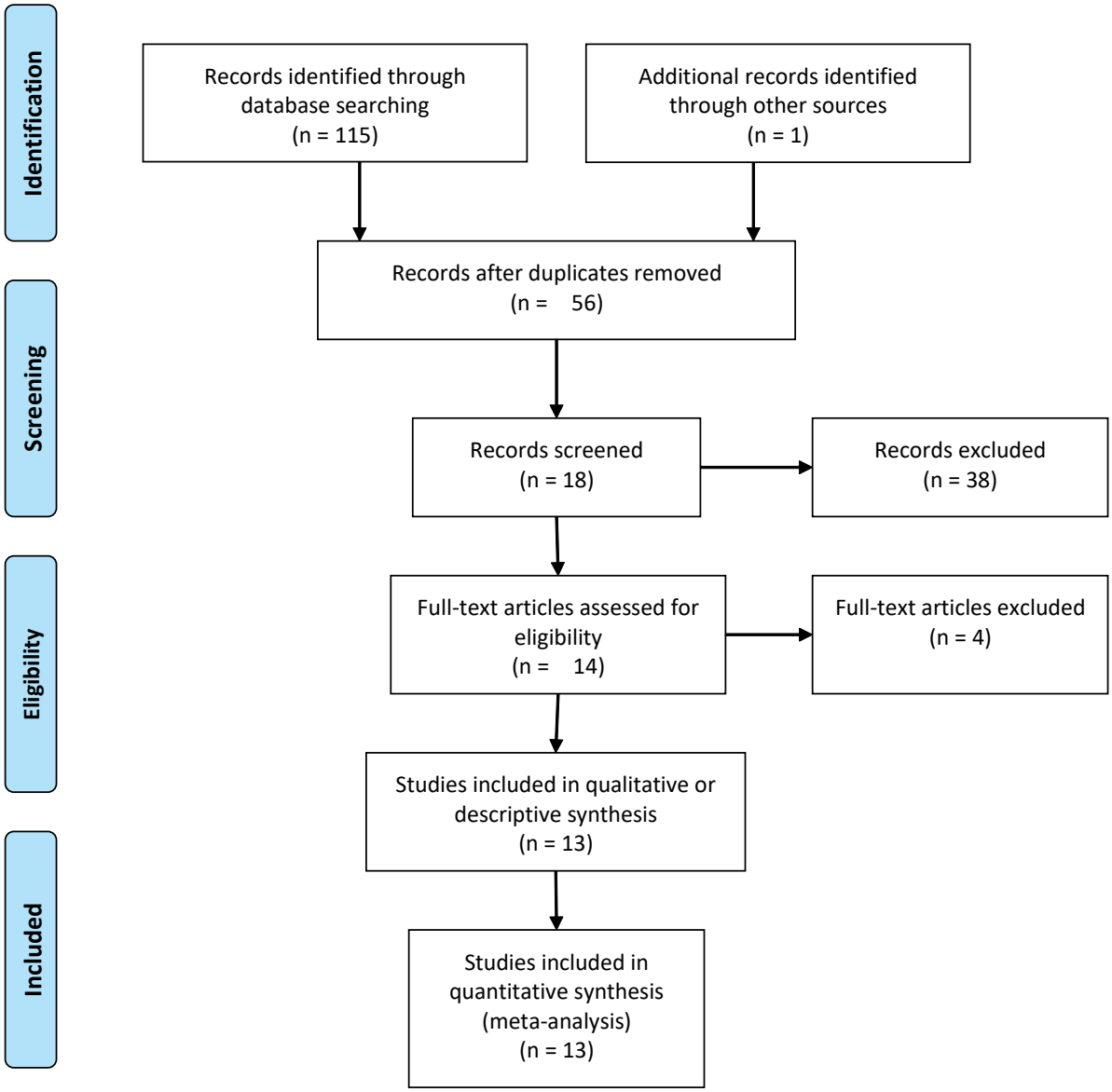

Supplementary Figure 1. PRISMA flow diagram

Supplementary Table 1.

Country/ Region	Banking	Births
Singapore	30,00%	39,039
Greece	10,00%	88,553
Portugal	10,00%	87,02
Puerto Rico	9,50%	21,4
Romania	7,00%	188,755
Taiwan	7,00%	181
South Korea	6,80%	326,9
Slovakia	6,00%	57,639
Hungary	5,00%	89,807
Serbia	5,00%	63,975
Hong Kong	3,50%	53,716
Montenegro	3,50%	7,264
Bosnia and Herzegovina	3,00%	29,328
Israel	3,00%	184,37
Poland	3,00%	396
Spain	3,00%	369,302
United Arab Emirates	3,00%	97,738
United States	3,00%	3788,24
Macedonia	2,90%	21,333
Slovenia	2,70%	19,585
South Africa	2,50%	1009,07
Canada	2,30%	382,533
Albania	1,50%	28,934
Lebanon	1,50%	128,687
Switzerland	1,50%	87,851
Australia	1,40%	315
Iran	1,20%	1366
China	1,00%	15230

Country/ Region	Banking	Births
Georgia	1,00%	51,138
Italy	1,00%	440,78
Japan	0,80%	918,4
Argentina	0,70%	685,394
Austria	0,70%	85,54
Colombia	0,70%	649,115
Croatia	0,70%	36,945
Ecuador	0,70%	293,139
Germany	0,70%	787,6
Peru	0,70%	60,5
Philippines	0,70%	1618,31
Malaysia	0,60%	501,945
Ukraine	0,57%	335,874
Denmark	0,50%	61,476
Jordan	0,50%	207,917
Norway	0,50%	55,12
Sweden	0,50%	115,832
Thailand	0,50%	666,109
Vietnam	0,50%	1472
India	0,40%	26028,1
Mexico	0,40%	2162,53
Brazil	0,36%	2870
Czech Republic	0,36%	114,036
Turkey	0,35%	1250
Belgium	0,30%	117,8
Russia	0,30%	1604,34
United Kingdom	0,30%	731,21
France	0,08%	758