

Umbilical cord banking in Italy

REPORT 2023

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Thanks to all of cord blood banks for availability

BACKGROUND

Hematopoietic stem cells (HSCs) contained in the umbilical cord blood (UCB), as well as in the bone marrow and peripheral blood, are progenitor cells that are able to differentiate into all types of blood cells (red blood cells, white blood cells and platelets). For this reason, HSCs are used for hematopoietic stem cell transplantation: this is a **consolidated life-saving procedure** treating several congenital and acquired hematological diseases, immunodeficiencies and metabolic disorders.

Cord blood donation is a strategic goal of the Italian National Health Service (SSN, Servizio Sanitario Nazionale). In Italy, collection and banking of UCB are carried out by non-profit public cord blood banks (CBBs).

IN ITALY, IT IS ALLOWED TO PERFORM:

- Collection and banking of UCB for “unrelated use”, i.e. for solidaristic purposes;
- Collection and banking of UCB “for autologous use” when the newborn has a specific pathology in progress at the time of the birth or highlighted in the prenatal period, or “for allogeneic related use” when one relative (i.e. brother/sister) has a disease in progress at the time of collection or previously diagnosed, which could be treated with HSCs transplantation;
- Collection and banking of UCB “for autologous/allogeneic related use” when families that are at risk of having children affected by genetically diseases (i.e. thalassemia) which could be treated with HSCs transplantation;
- Collection and banking of UCB “for autologous use” for experimental clinical trials, approved by current laws, also aimed at collecting scientific evidence of a possible new applications of UCB in given pathologies.

IN ITALY, IT IS NOT ALLOWED TO PERFORM:

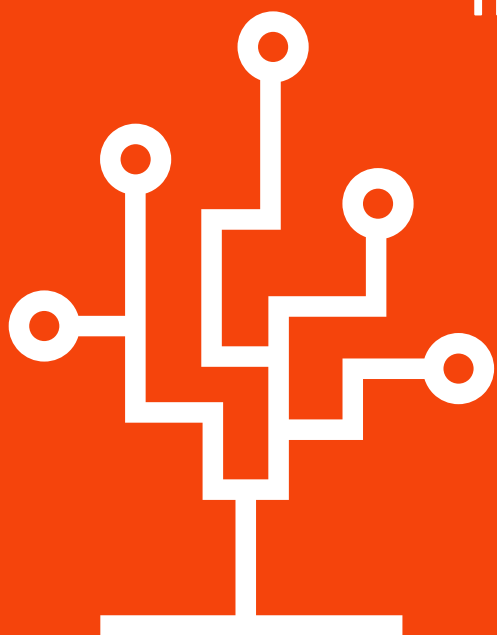
- Banking for exclusive autologous use (intra-familial
- or private use), when there are not present the abovementioned
- clinical conditions;
- The establishment of private CBBs on the national territory;
- Any type of advertising related to private banks in the public hospitals.

However, the collection of the UCB for private use and its export to foreign CBBs **is allowed**.

AIM OF THE REPORT

This report describes the data related to the activities of the Italian CBBs in 2023. The Italian network (ITCBN, Italian Cord Blood Network), which is the technical network of all Italian public CBBs, is coordinated by the National Blood Center (CNS, Centro Nazionale Sangue) in synergy with the National Transplant Center (CNT, Centro Nazionale Trapianti) for all aspects related to HSC transplantation.

ITALIAN CORD BLOOD NETWORK (ITCBN)



The no-profit public banks are organized in a network aimed at collection, banking and distribution of UCB. The network is authorized by Ministerial Decree on November 18, 2009, which defines the purposes and general organization. The ITCBN is aimed at creating the necessary links between public CBBS, and also at defining technical aspect related to cord blood eligibility, collection, banking and distribution of UCB for hematopoietic transplantation. The network currently includes 18 active public banks, localized in 13 Regions.

SISTRA-ITCBN

The activities of CBBs are collected and monitored by the CNS through the Italian national blood information system (SISTRA, Sistema Informativo dei Servizi TRAsfusionali) through a web-based application named SISTRA-ITCBN. SISTRA-ITCBN is the tool to evaluate the strategic goal defined by Law n.219, issued on October 21, 2005.

SISTRA-ITCBN permits to collect and process, at national level, activity data and information from CBBs related to:

- Data of the banks and collection centres (maternity wards performing UCB collection), including authorization and accreditation requirements;
- Data on collection, banking, storage and distribution of units for allogeneic and autologous/allogeneic related use;
- Update of the characteristics of the UCB national inventory.

HSC TRANSPLANTATION AND IBMDR

Search and reservation activities of the HSC units available for transplantation are coordinated by the Italian Bone Marrow Donor Registry (IBMDR) located at the Galliera Hospital in Genoa. In 2001, by the power of the law n.52, IBMDR has been officially recognized as the Italian registry of bone marrow donors as well as the other establishments in European and non-European countries.

The IBMDR also coordinates the activities of the regional donor registries. In 2006, a national agreement between regional and national government (Accordo Stato Regioni n. 2637, October 5, 2006 "Research and retrieval of hematopoietic stem cells in Italian and foreign registries and banks") recognized IBMDR as a "single point contact" for the search of HSCs, including umbilical cord blood, for transplantation purposes.



HSCS FROM UMBILICAL CORD BLOOD

Collection of HSCs from UCB is regulated by transfusion laws (Decree n. 219, October 21, 2005 regarding "New regulation of transfusion activities and the national production of blood products"). In Italy, all blood donations are based on the principle of voluntary, unpaid, anonymous, responsible and non-profit donation of human blood and its products, including HSCs.

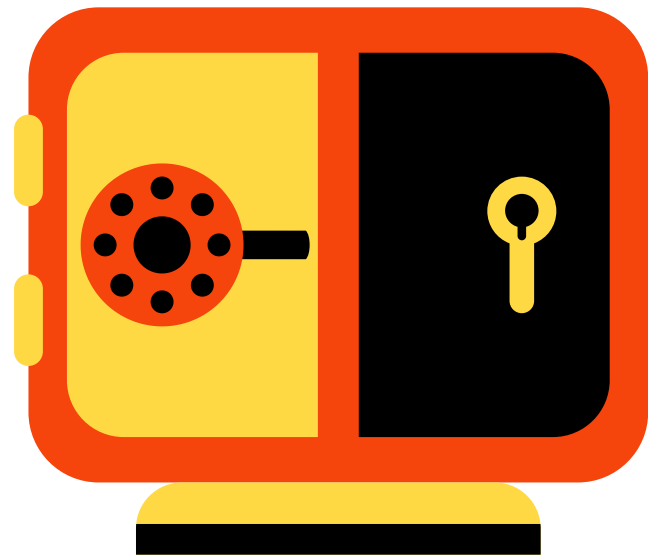
Regulatory and technical aspects concerning the collection, banking and storage of the UCB for autologous and allogeneic-related uses are established in the Ministerial Decree November 18, 2009 ("Indications for the storage of stem cells from umbilical cord blood for autologous use"). This decree allows public banks to perform collection, banking and storage of the UCB for autologous and allogeneic-related uses in case of actual or future clinical condition in which UCB banking is appropriate and supported from consolidated scientific evidence.

In accordance with the principles of the Italian national health system, the decree does not allow the establishment of private banks for the storage of UCB and any type of advertising related to private banks in public hospitals.

The activities relating to selection, collection, processing, validation, storage and distribution of the UCB, as well as the management of the CBB are also regulated by the Ministerial Decree November 2, 2015 ("Indications for the quality and safety requirements of the blood and blood components") and by Legislative Decree n. 16 January 25, 2010 ("Implementation of Directives 2006/17/EC and 2006/86/EC, which implements Directive 2004/23/EC as regards the technical requirements for donation, the procurement and control of human tissues and cells, as well as with regard to the traceability requirements, the notification of reactions and serious adverse events and certain technical requirements for coding, processing, preservation, storage and the distribution of human tissues and cells").

CORD BLOOD BANKS

Cord blood banks are identified as tissue establishment in accordance to Legislative Decree n. 191 November 6, 2007 (“Implementation of Directive 2004/23/EC on the definition of quality and safety standards for the donation, procurement, control, processing, storage and distribution of human tissues and cells”). In accordance with the article 6 of abovementioned decree, the CBB must be authorized and accredited by the government of the Regions and Autonomous Provinces. Structural, technological and organizational requirements for CBBs have been defined in a national agreement between regional and national government (Accordo Stato Regioni n. 184, October 29, 2009 and later updated in a subsequent Agreement on April 20, 2011 (“Guidelines for the accreditation of Umbilical Cord Blood Banks”).



For further details on regulations, refer to www.centronazionalelesangue.it on section “Attività”. “Sangue Cordonale”

DEFINITIONS

Allogenic: obtained from another individual. In the context of transplantation, it is defined as allogeneic transplant (or allograft), the procedure through which the recipient receives cells from a related or unrelated donor.

Autologous: derived and intended for the same individual. In the context of transplantation, it is defined as autologous transplant, the procedure through which the patient is transfused hematopoietic stem cells previously taken from himself.

Cord Blood Bank (CBB): facility where umbilical cord blood units are stored. It is made up of an integrated team, under the responsibility of the Bank's director, who is responsible for the collection, processing, characterization, cryopreservation, storage, release and distribution activities.

Collection Center (CC): the location under the responsibility of a single CBB where the activities of selection of the donors, if applicable, and the collection of the UCB units are carried out.

Hematopoietic stem cells (HSCs): adult stem cells that can self-regenerate and differentiate into the cellular elements of the blood (red blood cells, white blood cells and platelets). The sources of hematopoietic stem cells are bone marrow (mainly pelvic bones), peripheral blood, after stimulation with growth factors, and umbilical cord blood.

Human Leukocyte Antigen (HLA): antigens expressed by numerous cell types, including leukocytes, which have antigenic capacity and they are capable to stimulate the production of antibodies when presented to a recipient who does not express them. In the context of transplants, the typing of the antigens of the HLA system allows to define the compatibility between genetically related and non-genetically related individuals.

Umbilical cord blood (UCB): blood contained within the placenta and the vessels (vein) of the umbilical cord. It is one of the sources of hematopoietic stem cells and can be collected after the baby is born.

Umbilical cord blood unit: blood obtained from the placenta and from the vessels (vein) of the umbilical cord of a single placenta after the umbilical cord has been clamped. It is possible to collect the following types of units:

- allogeneic (AlloNF) unit: umbilical cord blood unit collected for allogeneic transplantation from an unrelated donor;
- allogeneic-related (AlloD) unit: umbilical cord blood unit collected for allogeneic transplantation from a family or related donor;
- autologous (Auto): umbilical cord blood unit collected for autologous transplantation.

HIGHLIGHTS



ITCBN currently consist of 18 CBB and 269 CC located in all Italian regions.

The childbirths carried out in the collection centers represent 64% of the total childbirths in Italy (2023: estimated data).



At the end of 2023, 38,401 allogeneic UCB units are available for transplantation (data from IBMDR)

At the end of 2023, 29% of UCB units have a total cell content greater than $150 \cdot 10^7$.

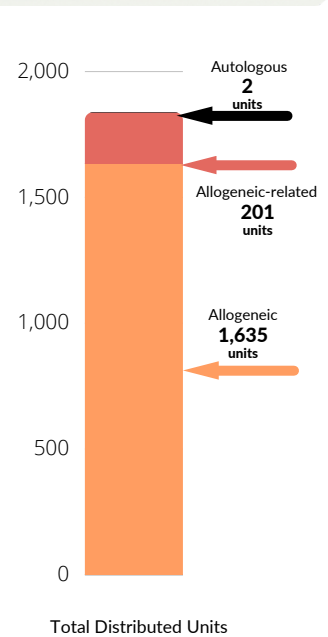
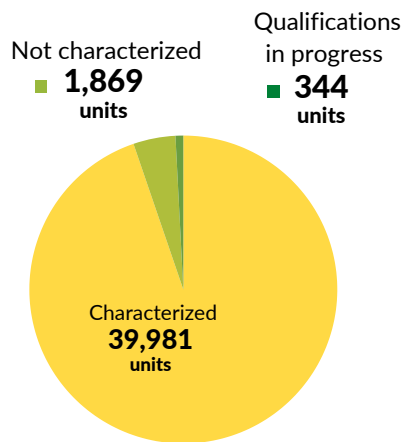
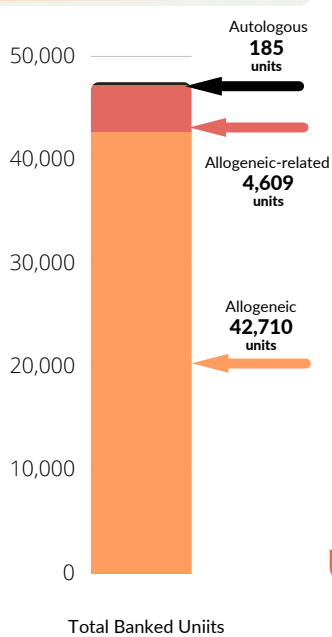
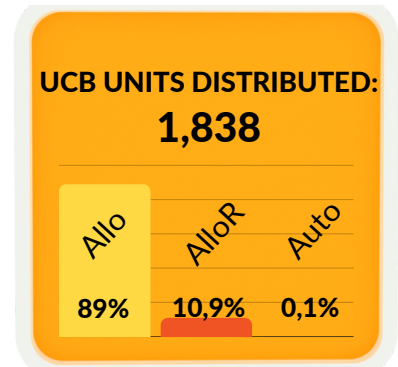
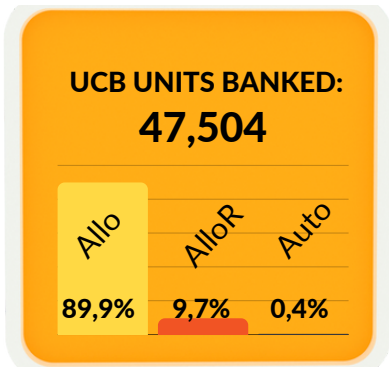


At the end of 2023, 4,609 allogeneic-related and 185 autologous units are available for transplantation.

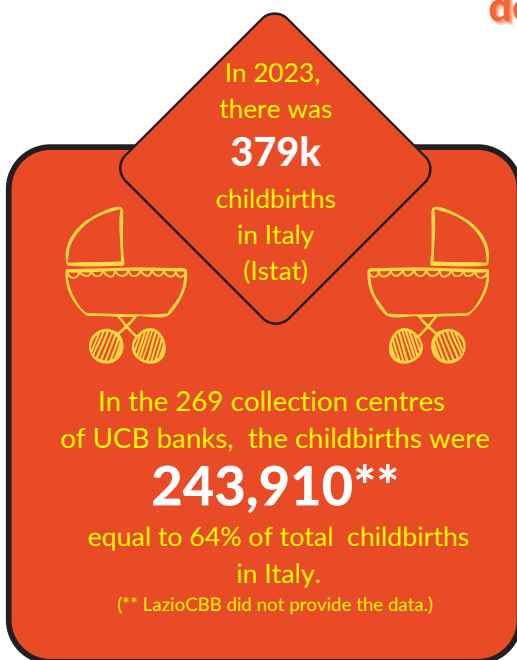
At the end of 2023, 1,635 allogeneic UCB units, 201 allogeneic-related and 2 autologous UCB units have been distributed.



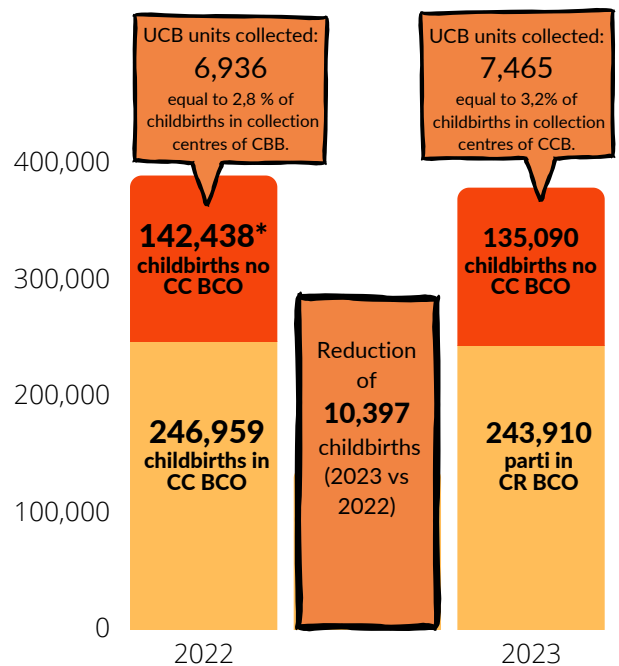
2023 ACTIVITIES



Umbilical cord blood units Correlation with demographic index



*Liguria did not provide the data.



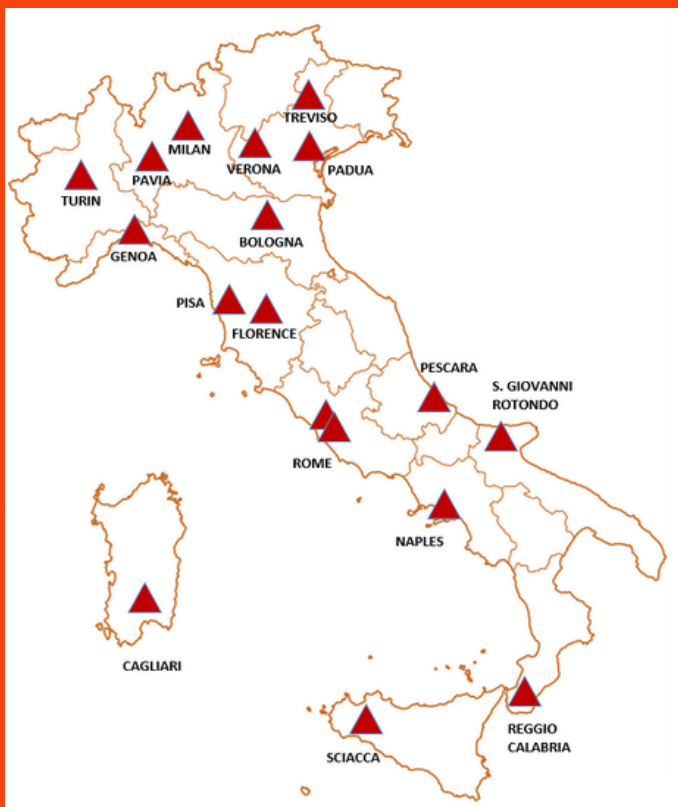
ORGANIZATION OF THE NETWORK

The ITCBN is the Italian network of CBBs authorized to collect, process, store and distribute cord blood units for allogeneic, allogenic-related and autologous purposes.

Currently, there are 18 active banks located in public or private hospitals operating in agreement with the Italian National Healthcare Service (NHS). These CCBs are in 13 Regions while CCs are in all Regions.

Veneto, Lombardy, Tuscany and Lazio regions have more than one bank (three banks in Veneto and two in the other regions, respectively) (fig. 1).

NETWORK



- 1.Turin Cord Blood Bank (Turin, Piedmont)
- 2.Milan Cord Blood Bank (Milan, Lombardy)
- 3.Verona Cord Blood Bank (Verona, Veneto)
- 4.Treviso Cord Blood Bank (Treviso, Veneto)
- 5.Liguria Cord Blood Bank (Genoa, Liguria)
- 6.Pavia Cord Blood Bank (Pavia, Lombardy)
- 7.Padua Cord Blood Bank (Padua, Veneto)
- 8.Emilia Romagna Cord Blood Bank (Bologna)
- 9.Pisa Cord Blood Bank (Pisa, Tuscany)
- 10.Florence Cord Blood Bank (Florence, Tuscany)
- 11.Lazio Cord Blood Bank (Rome, Lazio)
- 12.UNICATT Cord Blood Bank (Rome, Lazio)
- 13.Pescara Cord Blood Bank (Pescara, Abruzzo)
- 14.BA.S.C.O. Campania (Naples, Campania)
- 15.Apulia Cord Blood Bank (San Giovanni Rotondo, Foggia, Apulia)
- 16.Calabria Cord Blood Bank (Reggio Calabria, Calabria)
- 17.Sciacca Cord Blood Bank (Sciacca, Agrigento, Sicily)
- 18.Cagliari Cord Blood Bank (Cagliari, Sardinia).

The characteristics of the banks of the Italian network are illustrated in table 1.

In terms of certifications and accreditations, all CBBs have the regional accreditation and an EFI/ASHI accredited laboratory that performs HLA typing. They all cooperate with IBMDR for all activities related to the distribution of UCB units to Italian and foreign Transplant Centers.

| | CCB ACRONYMS | REGIONS | BEGINNING OF ACTIVITY (YEAR) | ISO/VISION CERTIFICATION | NETCORD/FACT ACCREDITATION |
|--------------------------------|--------------|----------------|------------------------------|--------------------------|----------------------------|
| PESCARA CORD BLOOD BANK | PECBB | Abruzzo | 1997 | ✓ | ✓ |
| CALABRIA CORD BLOOD BANK | Calabria CBB | Calabria | 2006 | ✓ | |
| BA.S.C.O. CAMPANIA | BASCO | Campania | 1996 | ✓ | |
| EMILIA ROMAGNA CORD BLOOD BANK | ERCBB | Emilia Romagna | 2001 | ✓ | ✓ |
| LAZIO CORD BLOOD BANK | LAZIO CBB* | Lazio | 1994 | | ✓ |
| UNICATT CORD BLOOD BANK | UNICATTCBB | Lazio | 1999 | ✓ | ✓ |
| LIGURIA CORD BLOOD BANK | LiguriaCBB* | Liguria | 1997 | ● | ● |
| MILAN CORD BLOOD BANK | MICBB | Lombardy | 1993 | ✓ | ✓ |
| PAVIA CORD BLOOD BANK | PVCBB | Lombardy | 1997 | ✓ | |
| TURIN CORD BLOOD BANK | TOCBB | Piedmont | 1990 | ✓ | |
| APULIA CORD BLOOD BANK | PugliaCBB | Apulia | 2008 | ✓ | |
| CAGLIARI CORD BLOOD BANK | CCBB | Sardinia | 2011 | ✓ | |
| SCIACCA CORD BLOOD BANK | SciaccaCBB | Sicily | 2008 | ✓ | 2017 |
| FLORENCE CORD BLOOD BANK | FICBB | Tuscany | 1996 | ✓ | |
| PISA CORD BLOOD BANK | PICBB | Tuscany | 2004 | ✓ | |
| TREVISO CORD BLOOD BANK | TVCBB | Veneto | 1996 | ✓ | ✓ |
| VERONA CORD BLOOD BANK | VRCBB | Veneto | 2008 | ✓ | |
| PADUA CORD BLOOD BANK | PDCBB | Veneto | 1992 | ✓ | |

Table 1. CBB data and characteristics (Beginning of activity, Certification ISO / Vision and Accreditation NetCord / FACT)

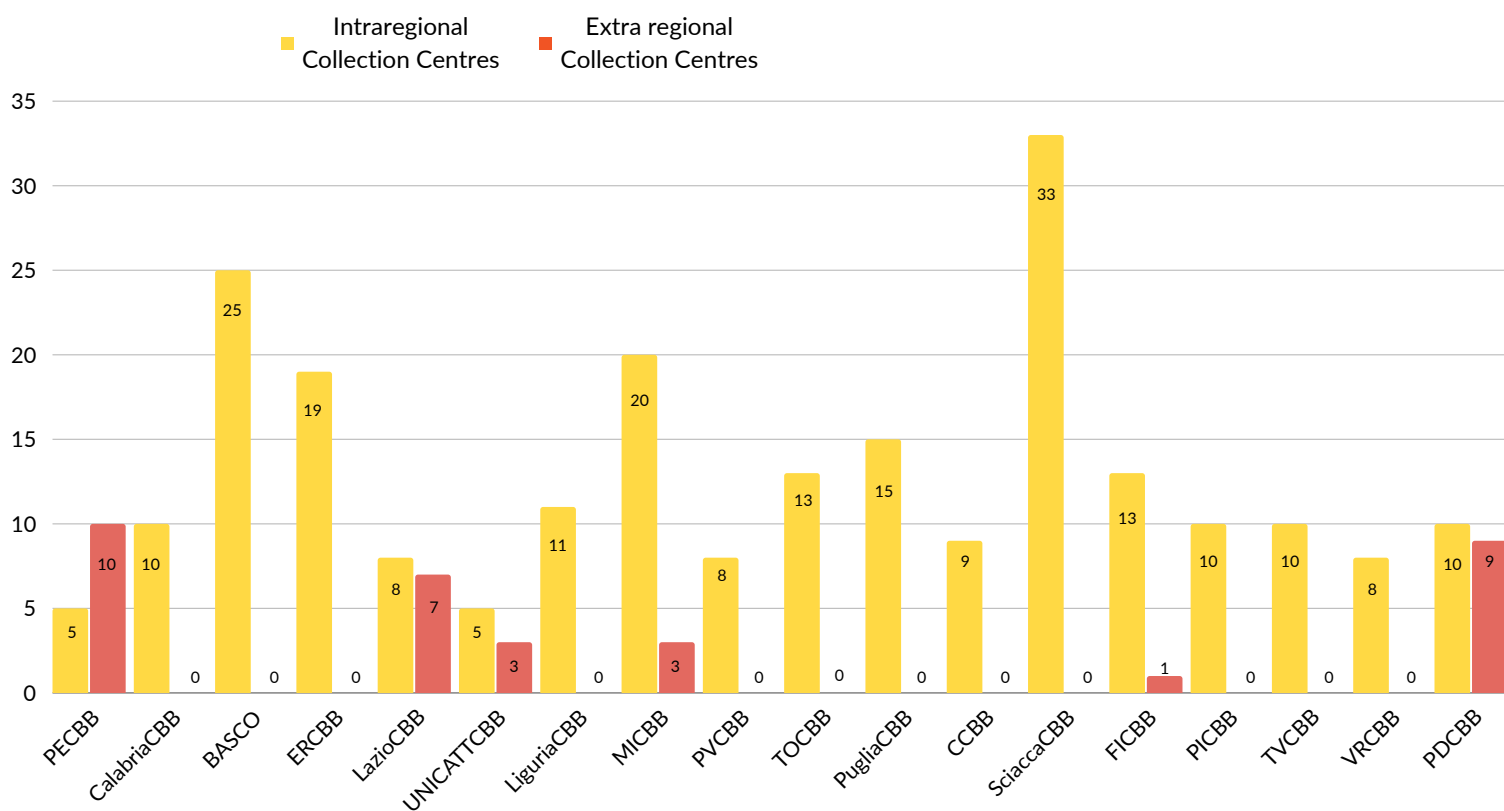
*Liguria currently suspended. Lazio CBB Netcord/Fact accredited until June 2023.

Since 2019, CNT/CNS audit have been scheduled for renewal of the compliance certification of the 18 CBB -ITCBN network. They have been carried out 6 audit on-site (2019 - early 2020) and, following the COVI-19 emergency, 10 documentary assessments (Table 2).

The collection of UCB units is carried out in the CC afferent to a single CBB. As illustrated in graph 1, 269 collection centers are currently active in Italy: 33 of these are present in regions without a CBB.

| | LAST CNS/CNT AUDIT (YEAR) | ASSESSMENT TYPE | CNS/CNT CERTIFICATION RENEWAL |
|---------------------|---------------------------|-----------------|-------------------------------|
| PECBB | 2019 | Documentary* | ✓ |
| CALABRIA CBB | 2020 | Documentary* | ✓ |
| BASCO | 2020 | On site | ✓ |
| ERCBB | 2019 | On site | ✓ |
| LAZIO CBB | 2020 | On site | ✓ |
| UNICATT CBB | 2023 | On site | ✓ |
| LIGURIA CBB | 2019 | --** | ● |
| MICBB | 2020 | Documentary* | ✓ |
| PVCBB | 2020 | Documentary* | ✓ |
| TOCBB | 2020 | Documentary* | ✓ |
| PUGLIA CBB | 2019 | On site | ✓ |
| CCBB | 2020 | Documentary* | ✓ |
| SCIACCACBB | 2021 | Documentary* | ✓ |
| FICBB | 2021 | Documentary* | ✓ |
| PICBB | 2020 | On site | ✓ |
| TVCBB | 2019 | Documentary* | ✓ |
| VRCBB | 2023 | On site | ✓ |
| PDCBB | 2019 | On site | ✓ |

Table 2. CNS/CNT audit of CBB (year of last audit, type of assessment, results. *Documentary assessment due to Covid-19 emergency. Liguria CBB currently suspended.



Graph 1. Histogram chart relating to operating collection center (intra- and extra-regional) for each CBB in 2023

Table 3. CBB with its extra regional collection centres.

| CBB Code | N° Extra Regional Collection Centres |
|-------------|---|
| PECBB | 10 Marche |
| LAZIO CBB | 4 Umbria 3 Basilicata |
| UNICATT CBB | 3 Molise |
| MICBB | 3 PA Trento |
| FICBB | 1 Umbria |
| PDCBB | 4 PA Bolzano 5 Friuli Venezia Giulia |

ACTIVITY DATA AND PERFORMANCE INDICATORS

In SISTRA-ITCBN, the activity data refer to the units collected, banked and distributed related to:

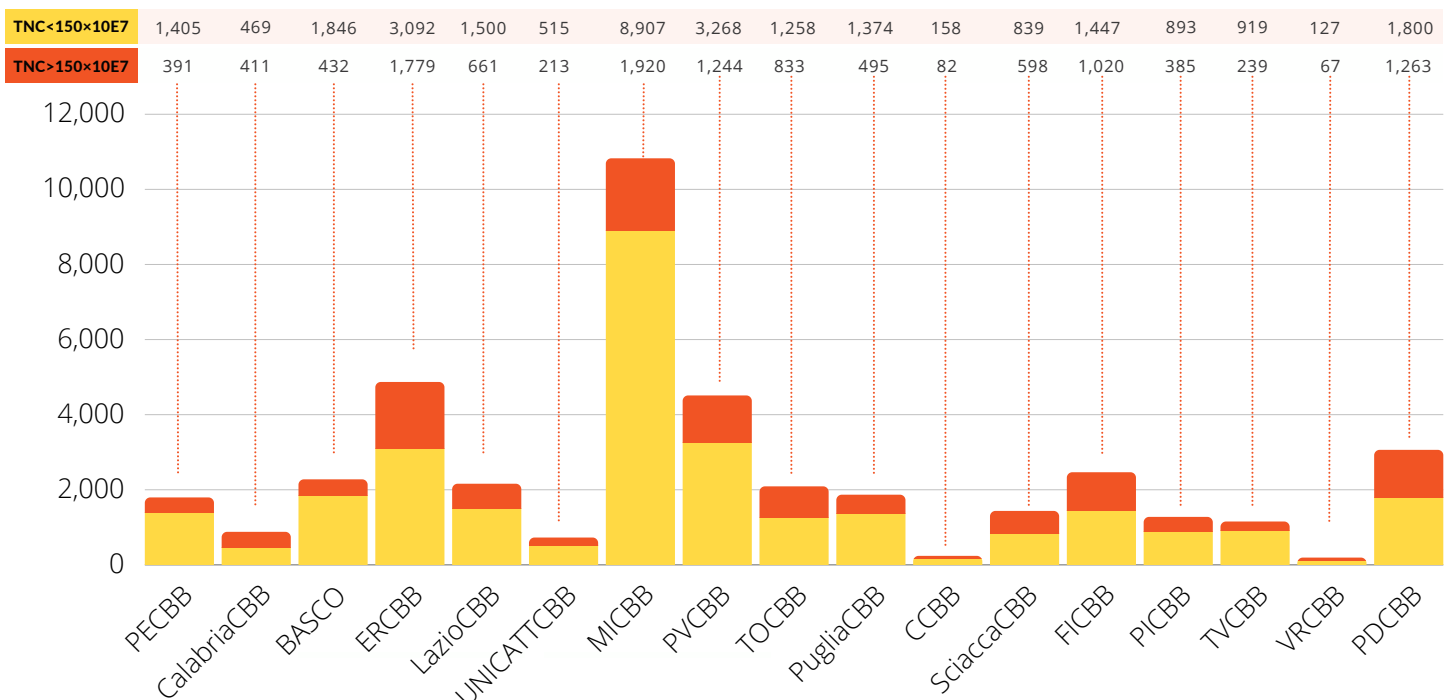
- A) Allogeneic unrelated units (ALLONF);
- B) Allogeneic-related units (ALLOD);
- C) Autologous units (Auto).

A) Allogeneic unrelated units (ALLONF)

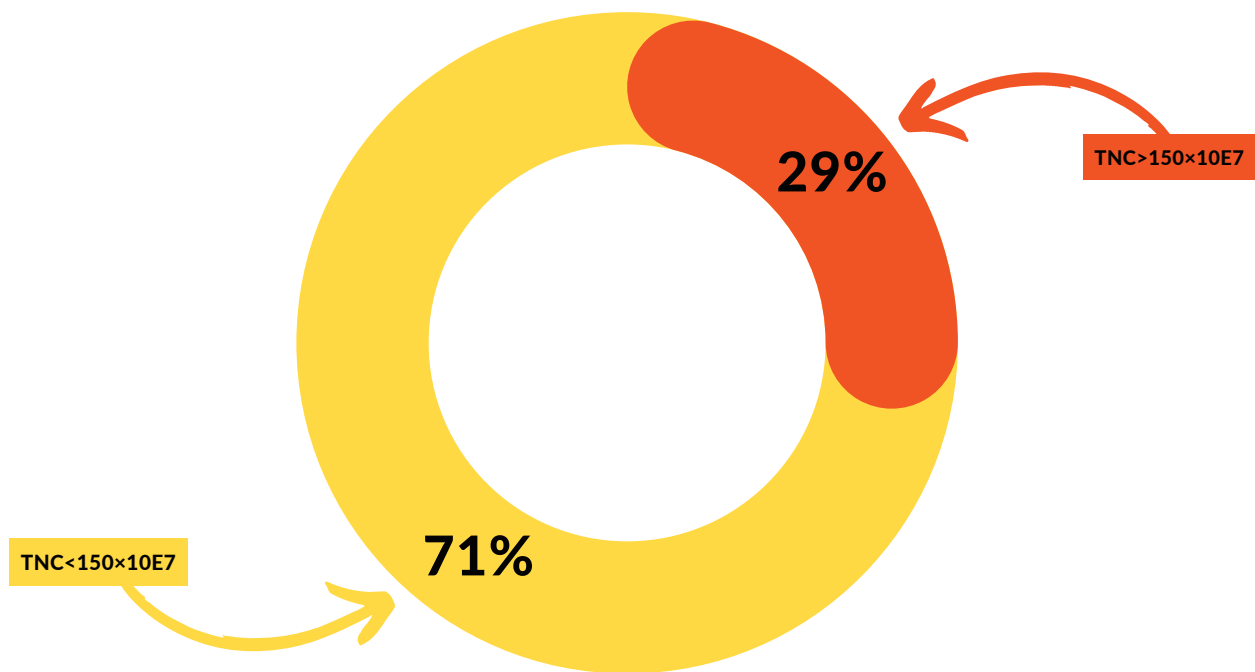
The inventory of cord blood units represents the total number of allogeneic unrelated units present in each bank. The parameters used to characterize the inventory of each bank are: the number of total nucleated cells (TNCs, total nucleated cells) sufficient to ensure the appropriate transplant dose, and the HLA characterization. Units with TNCs greater than 150×10^7 cells represent the inventory with high cellularity.

In the oldest CBBs, the inventory is made up of units with low cellularity due to the different banking criteria applied in the past. There is also an inventory quota with cellularity between $120-150 \times 10^7$ which represents UCB units banked in the period 2011-2016 and related to the introduction of a threshold of 120×10^7 cells. Graphs 2 and 3 show the data relating to the characteristics of the inventory in terms of:

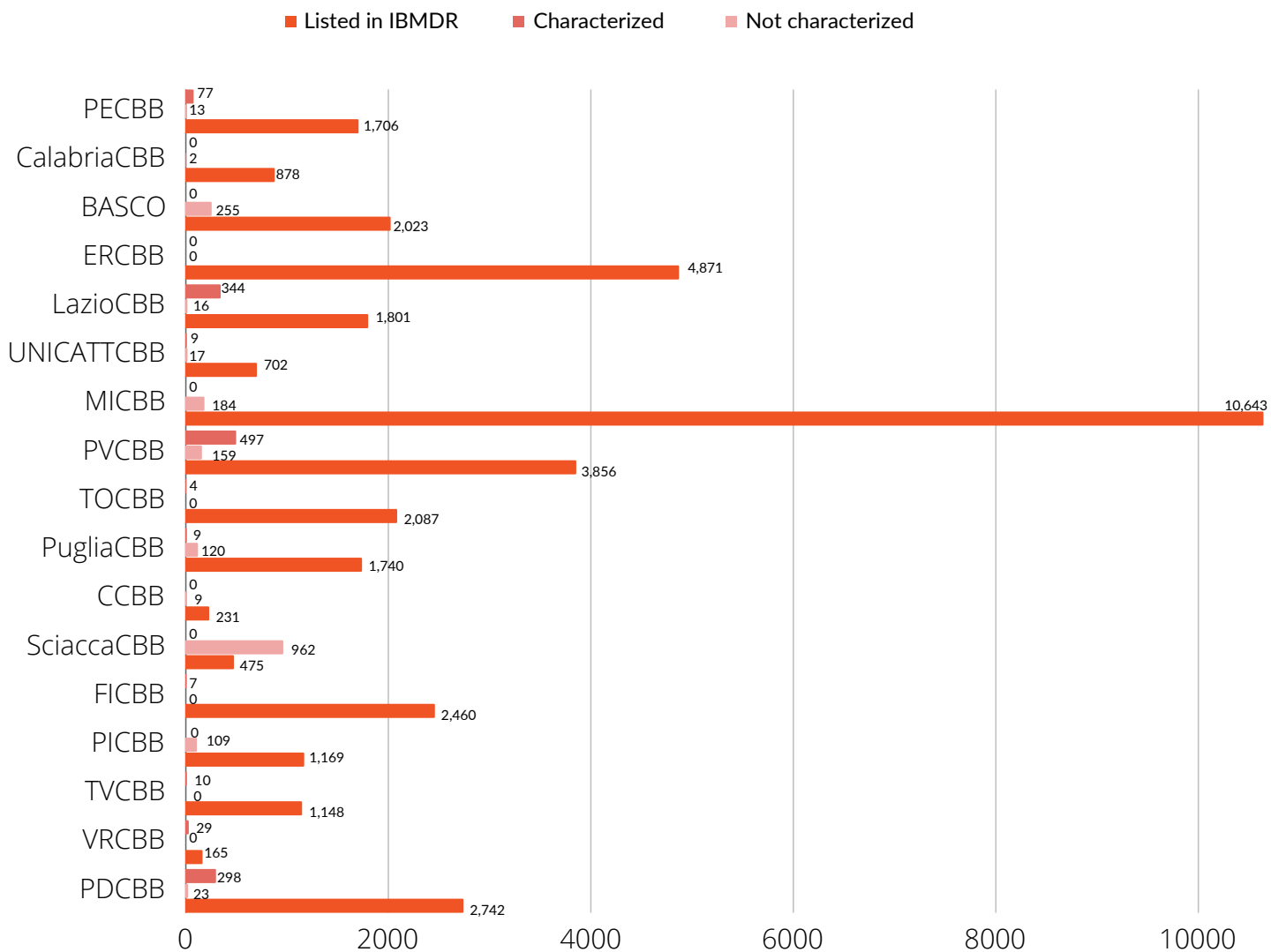
- Units with a higher TNC content ($TNC > 150 \times 10^7$): indicates the percentage of units with $TNC > 150 \times 10^7$ out of the total number of units in the inventory;
- Units to be characterized: indicates the percentage of units with HLA typing in progress compared to the total number of units in the inventory
- TNC content of units available for transplantation (expressed as $TNC \times 10^7$)



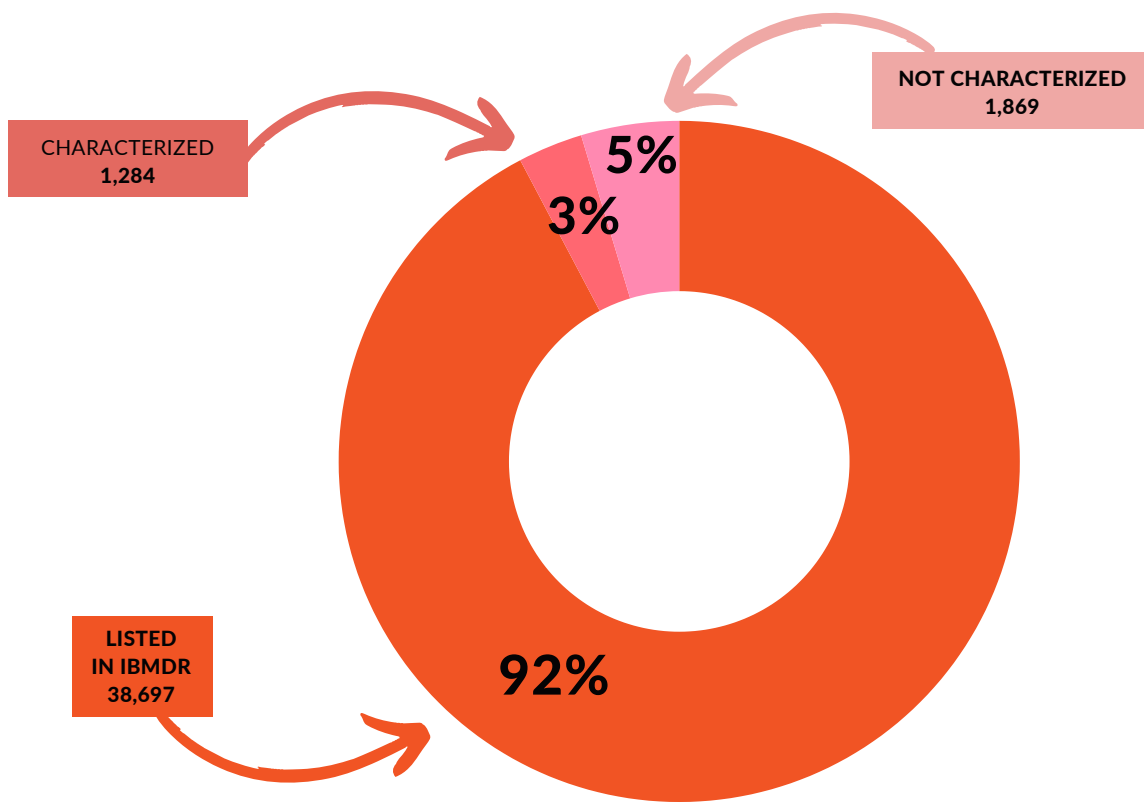
Graph 2. Histogram chart relating units with a high cellularity ($TNC > 150 \times 10^7$) for each CBB..



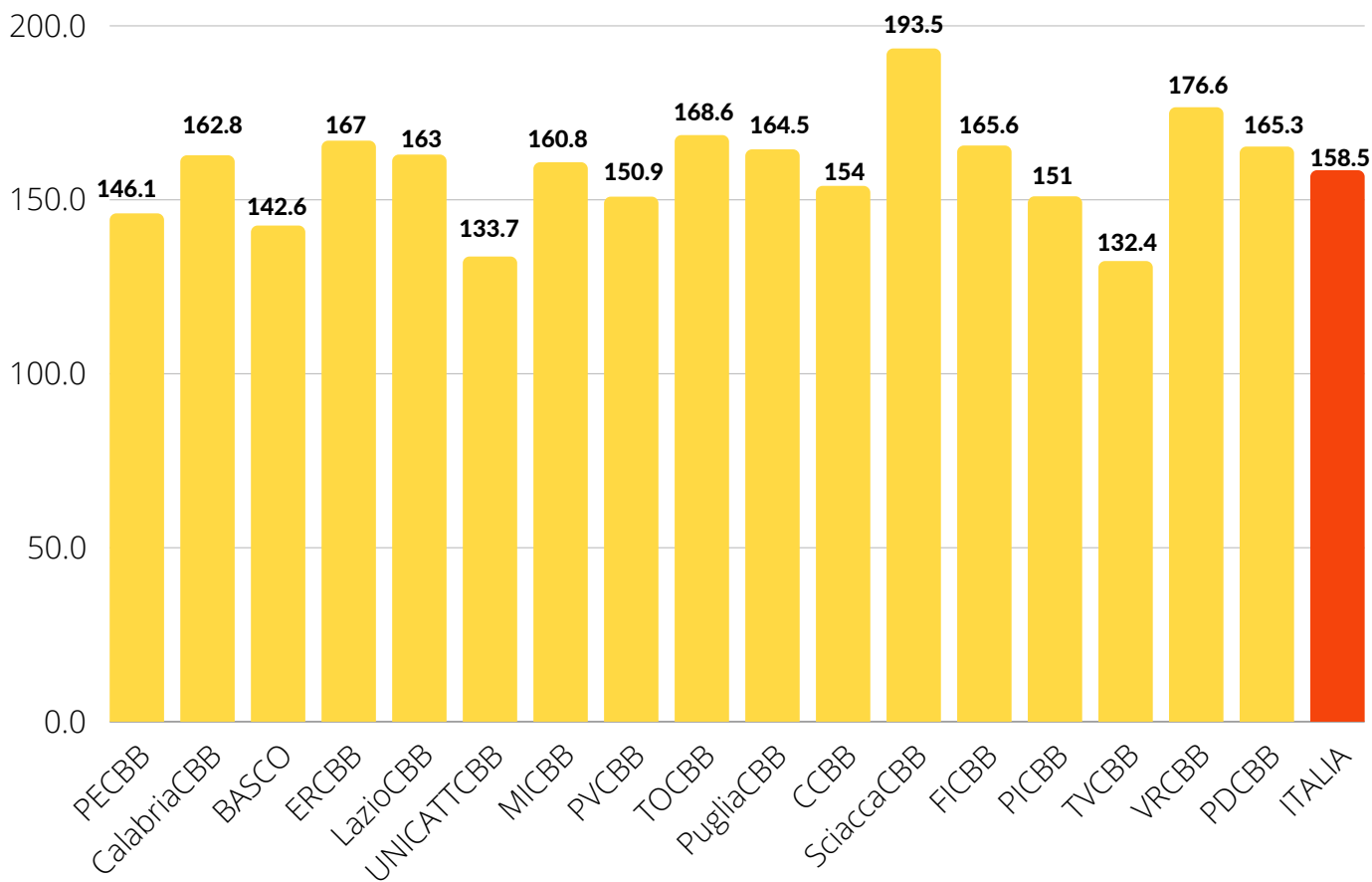
Graph 3. Donut chart relating to units relating units with a high cellularity (TNC > 150*10e7)



Graph 4. Histogram chart relating to units listed in the registry IBMDR, HLA characterize, and HLA not characterize for each CBB



Graph 5. Donut chart relating to units listed in the registry IBMDR, HLA characterize, and HLA non characterize national data.



Graph 6. Histogram chart relating to cellularity of UCB banked..

COLLECTION DATA AND BANKING INDEX (TOTAL AND FOR EACH CBB)

For the 2023 analysis, two types of indicators are used:

- quantitative indicators: they are capable of measuring the activities of each CBB;
- qualitative indicators: they are capable of measuring the bank's ability to promptly and adequately respond to search requests of UCB units. The qualitative indicators significantly influence the procedures of HSC unit selection at the transplant centers when multiple sources of HSCs are available.

The quantitative indicators included:

1. Total number of UCB units collected in the current the year (table 4);
2. Collection index (%): ratio between the number of collected units and the number of deliveries carried out in the collection center (graph 7);
3. Banking index (%): ratio between the number of banked units and the number of units collected (graph 8) and trend for the period 2007-2023 (graph 9);
4. Inventory index (%): ratio between the number of units listed in the registry (IBMDR) and the number of banked units (graph 10);
5. Distribution index: ratio between the number of units distributed on the number of units listed in the registry, and so potentially releasable.

| | COLLECTED | BANKED | DISTRIBUTED |
|--------------|-----------|--------|-------------|
| PECBB | 320 | 25 | 1 |
| Calabria CBB | 215 | 12 | 1 |
| BASCO | 270 | 17 | 0 |
| ERCBB | 828 | 39 | 0 |
| LazioCBB | 119 | 7 | 0 |
| UNICATTCBB | 306 | 27 | 0 |
| MICBB | 575 | 68 | 3 |
| PVCBB | 143 | 5 | 1 |
| TOCBB | 553 | 22 | 0 |
| PugliaCBB | 783 | 17 | 1 |
| CCBB | 274 | 11 | 0 |
| SciaccacBB | 1613 | 53 | 0 |
| FICBB | 474 | 7 | 2 |
| PICBB | 238 | 22 | 0 |
| TVCBB | 100 | 5 | 2 |
| VRCBB | 103 | 3 | 0 |
| PDCBB | 551 | 34 | 2 |

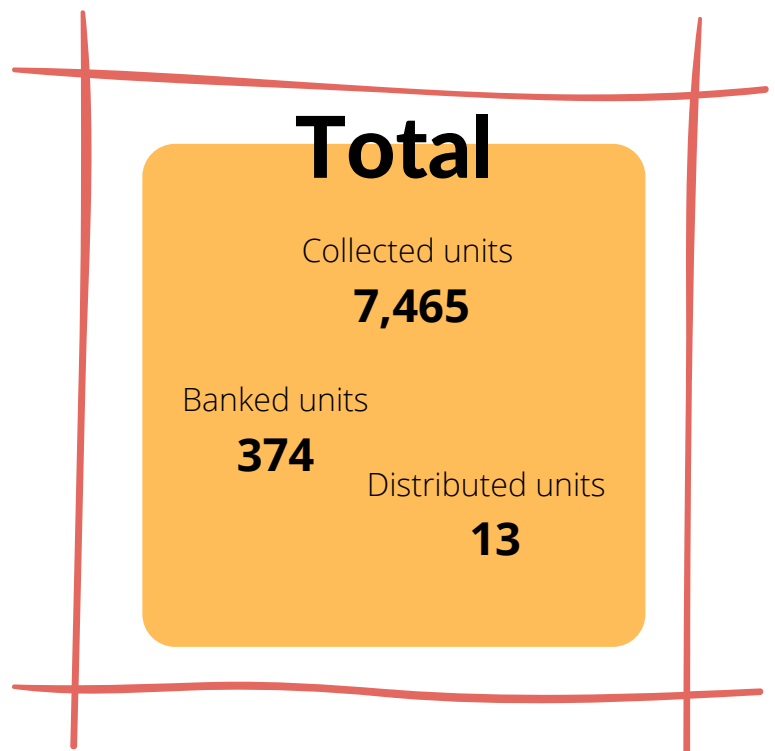
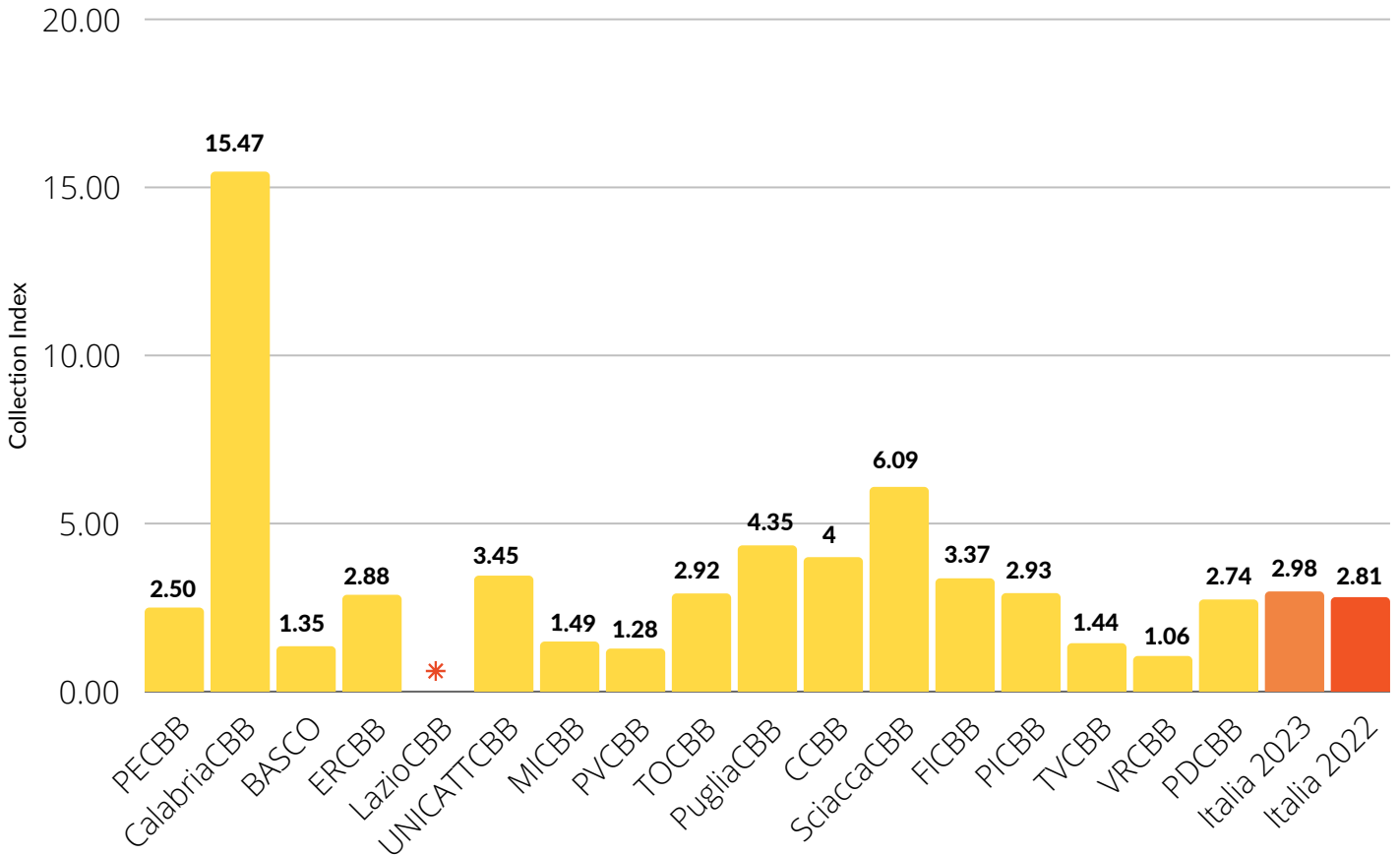
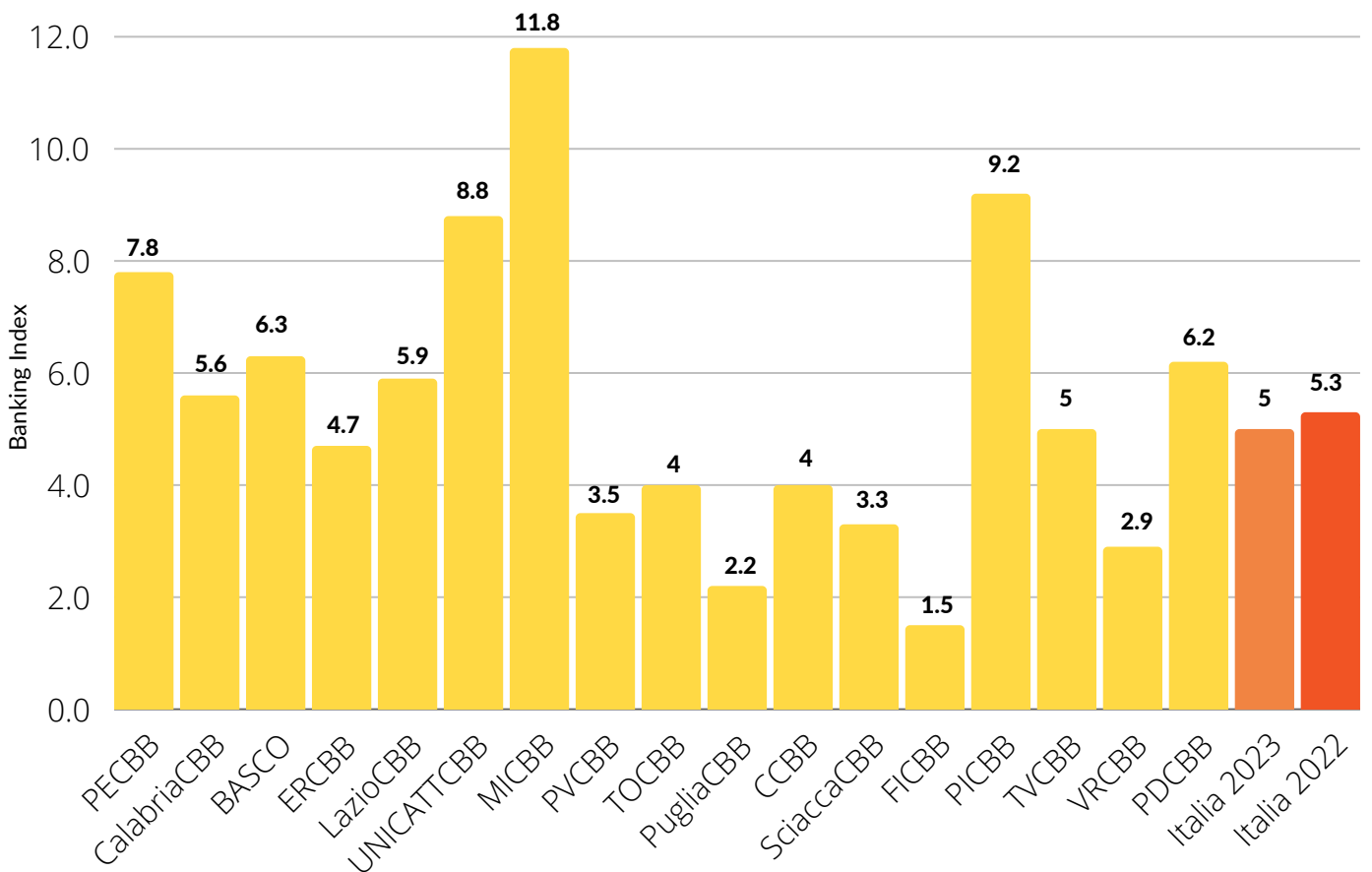


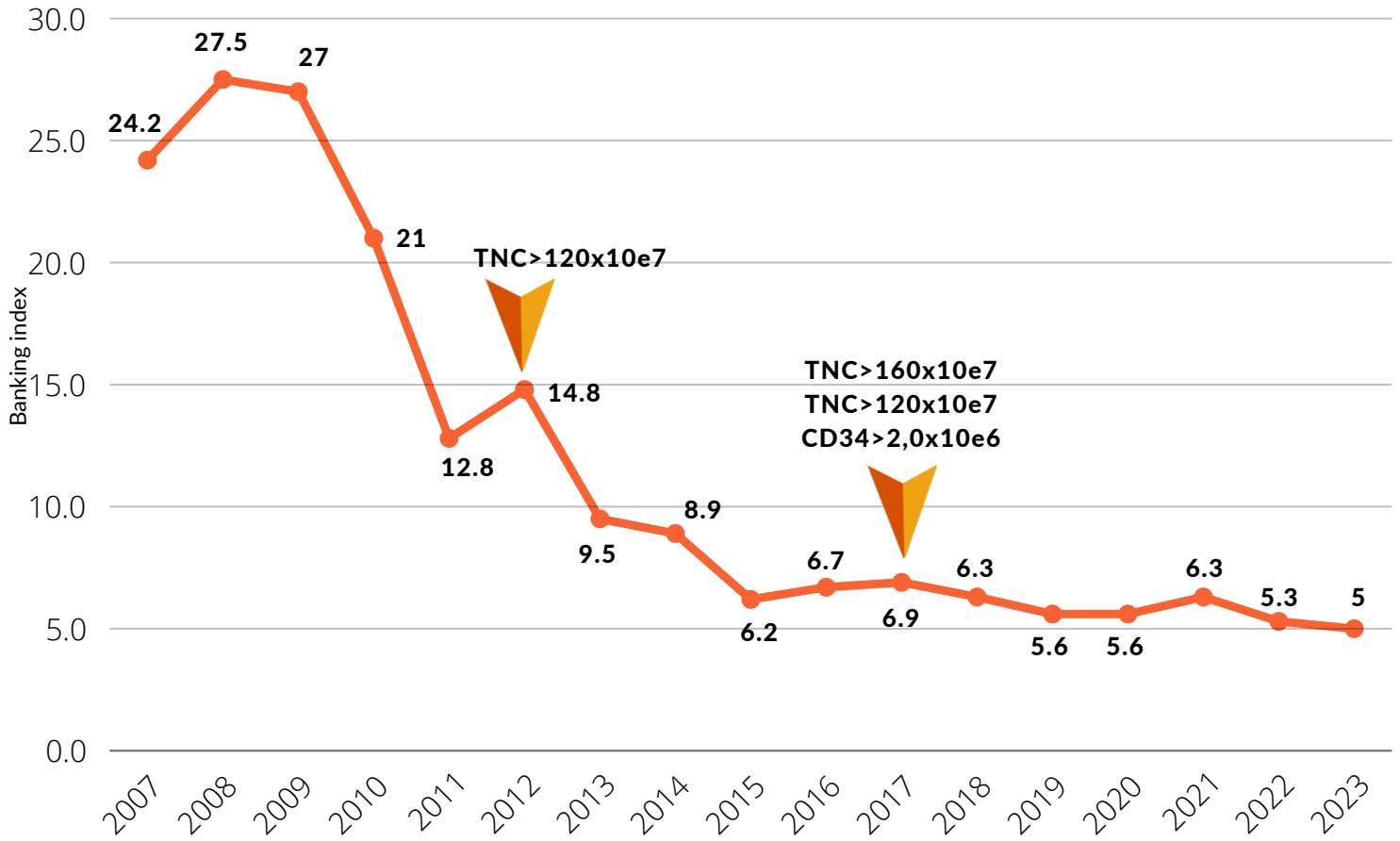
Table 4. Data of units Collected-Banked-Distributed – 2023.



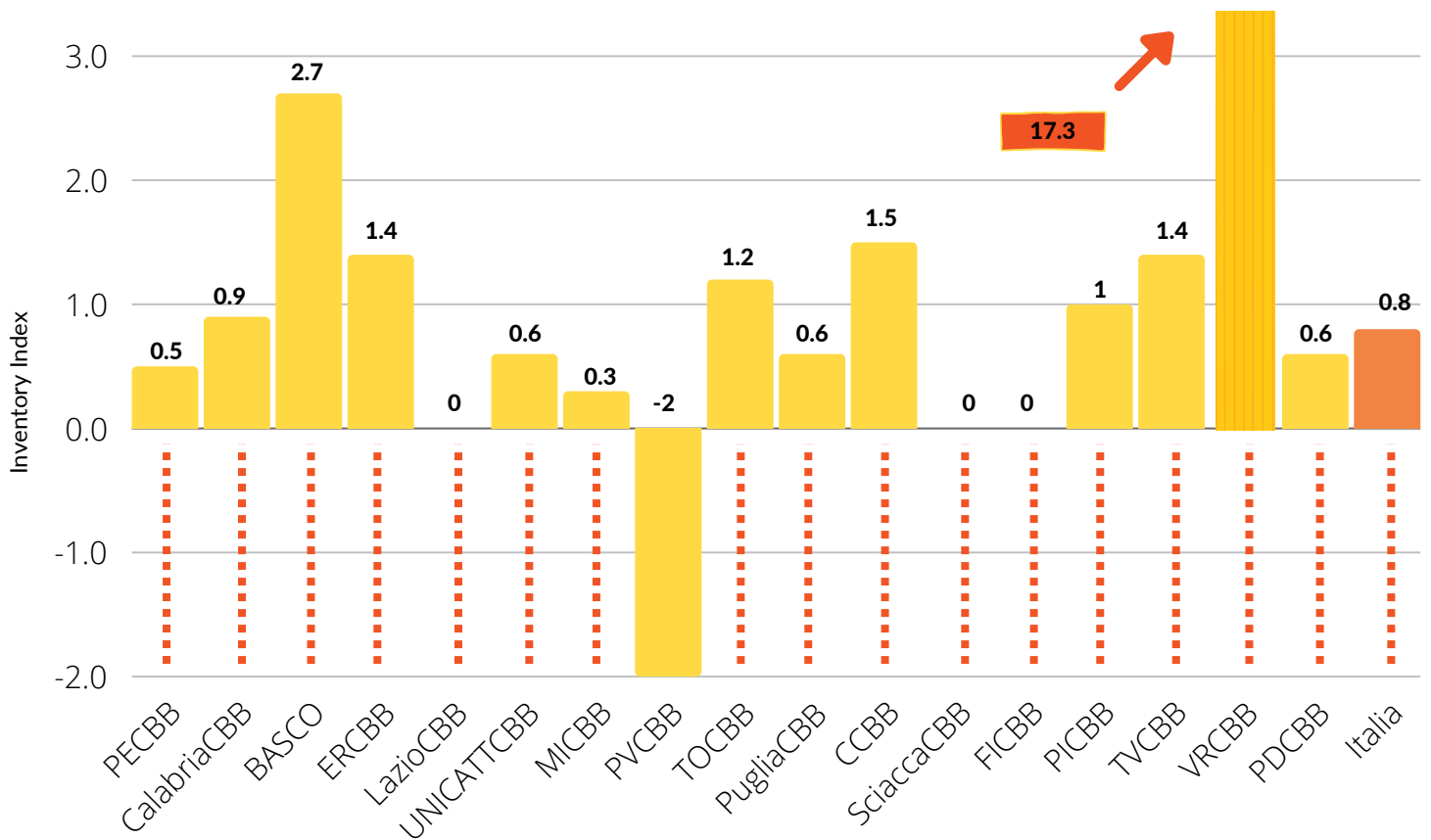
Graph 7. Histogram chart relating to collection index (No. collected units/ No. deliveries)
 *Partial data: the number of deliveries was not provided.



Graph 8. Histogram chart relating to banking index (No. banked units/No. collected units)



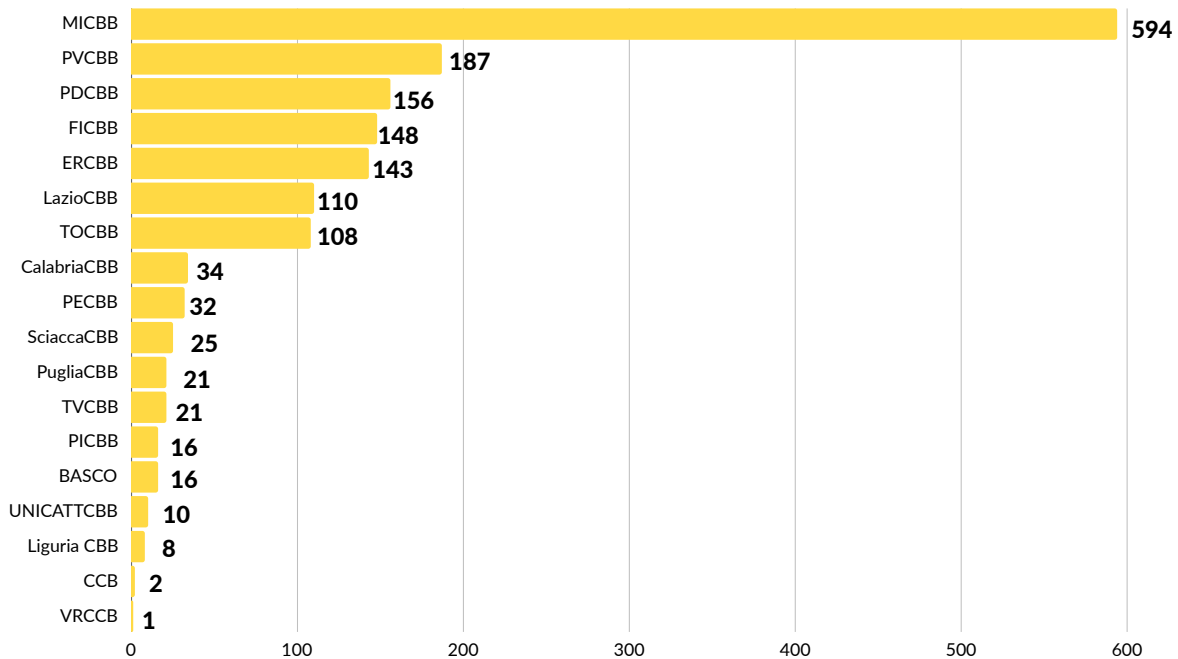
Graph 9. Trend of banking index 2007-2023 period



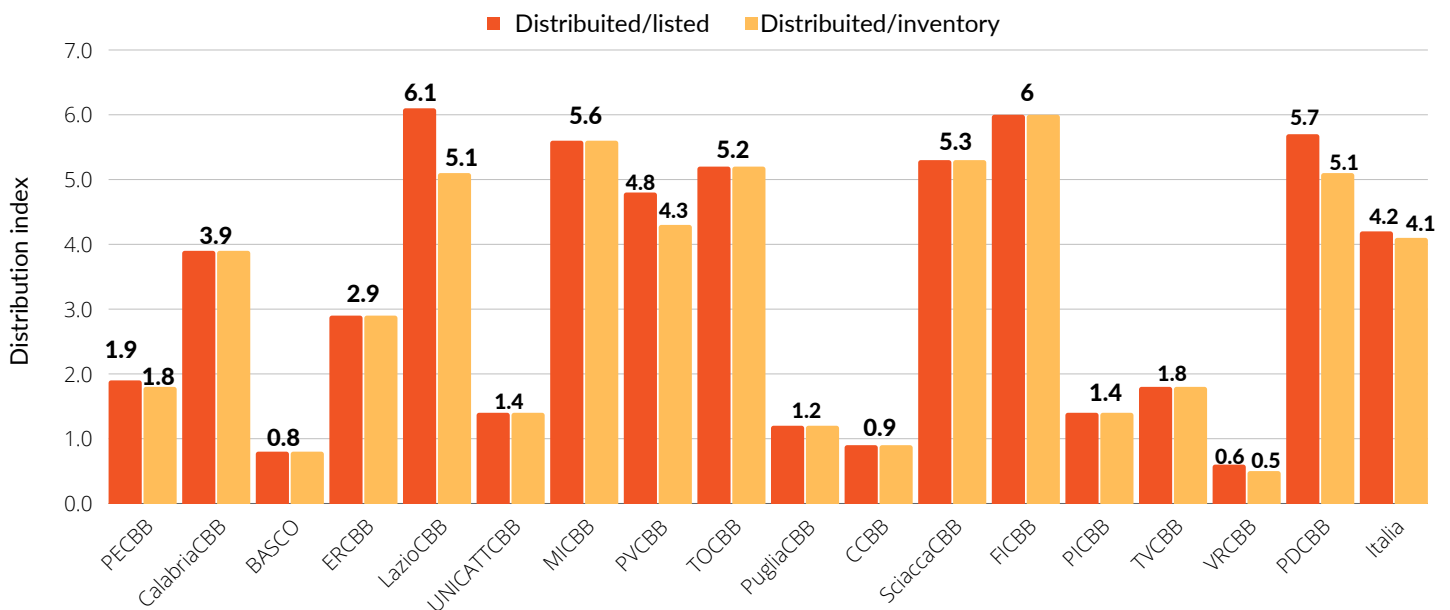
Graph 10. Histogram chart relating to inventory index (No. listed in registry units/ No. banked units) VRCBB has exposed in 2023 a number of Units characterized in the years before.

DISTRIBUTED UNITS AND DISTRIBUTION INDICES

The data related to distribution of UCB units are showed in an aggregate way in graph 11 (total number of the UCB units distributed at the end of December 2023) and as a percentage both in relation to the total number of the units in inventory and listed to the IBMDR (graph 12).



Graph 11. Histogram chart relating UCB units distributed.



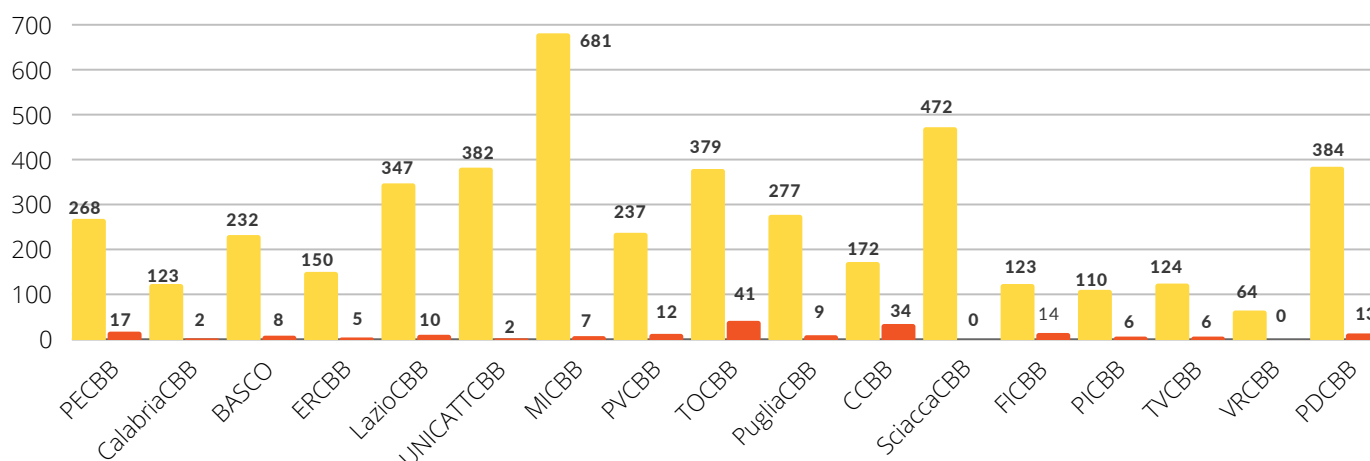
Graph 12. Histogram chart relating distribution index.

B) and C) allogeneic-related (ALLOD) and autologous (AUTO)

CBBs have in their inventory units for allogeneic-related or autologous use. The data reported the total number of the UCB units collected and banked in 2023 (table 5). Data related to the inventory of allogeneic-related and autologous allogeneic units are showed below (graph 13).

| Banche | N. UCB ALLOGENIC-RELATED UNITS | | | N. UCB AUTOLOGOUS UNITS | | |
|---------------|--------------------------------|-----------|-------------|-------------------------|----------|-------------|
| | COLLECTED | BANKED | DISTRIBUTED | COLLECTED | BANKED | DISTRIBUTED |
| PECBB | 2 | 2 | 0 | 0 | 0 | 0 |
| CalabriaCBB | 3 | 3 | 0 | 0 | 0 | 0 |
| BASCO | 1 | 1 | 0 | 0 | 0 | 0 |
| ERCBB | 1 | 1 | 0 | 0 | 0 | 0 |
| LazioCBB | 4 | 4 | 3 | 0 | 0 | 0 |
| UNICATTCBB | 16 | 12 | 0 | 0 | 0 | 0 |
| MICBB | 9 | 9 | 1 | 2 | 2 | 0 |
| PVCBB | 4 | 4 | 0 | 0 | 0 | 0 |
| TOCBB | 6 | 4 | 0 | 0 | 0 | 0 |
| PugliaCBB | 6 | 6 | 0 | 0 | 0 | 0 |
| CCBB | 8 | 8 | 0 | 5 | 5 | 0 |
| SciaccaCBB | 10 | 10 | 0 | 0 | 0 | 0 |
| FICBB | 1 | 1 | 0 | 1 | 1 | 0 |
| PICBB | 2 | 2 | 0 | 0 | 0 | 0 |
| TVCBB | 4 | 4 | 0 | 0 | 0 | 0 |
| VRCBB | 3 | 2 | 0 | 0 | 0 | 0 |
| PDCBB | 7 | 6 | 1 | 0 | 0 | 0 |
| Totale | 87 | 77 | 5 | 8 | 8 | 0 |

Table 5. Data relating to collected, banked, distributed units: allogeneic-related and autologous units- 2023



Graph13. Histogram chart related to inventory of UCB allogeneic-related and autologous units..

ALTERNATIVE USES

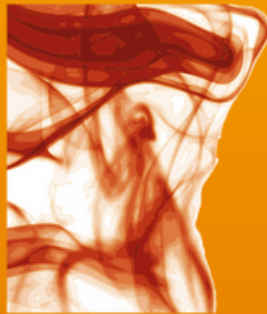
In addition to the banking activities for hematopoietic stem cell transplantation, some CBBs produce blood components for alternative use (red blood cells, platelet gel, serum drops, etc.) for the discarded material generated from CB banking operations (e.g. for low cellularity). Some of these uses are subject of experimental trials.

SPECIAL THANKS

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Furthermore, thanks are due to all the mothers and fathers who have donated the Umbilical cord blood of their children: this solidarity act has allowed the creation of an Italian inventory



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