Standardizzazione del prodotto leucoaferetico dal punto di vista tecnico

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Key issues in mobilization and separation techniques

A. Long-term evidence of safety and efficacy of G-CSF in mobilization of HPC

B. The option of Plerixafor addition to G-CSF in proven, predicted poor mobilizers or on demand

C. Safety and efficacy of apheretic collection of HPC, even in case of CVC use

Separation techniques to improve efficiency and efficacy (main characteristics)

A. Continuous flow separation, possibly at constant flow rate (not higher than 50/60 ml/min)

B. Low extracorporeal volume (particularly in pediatric procedures)

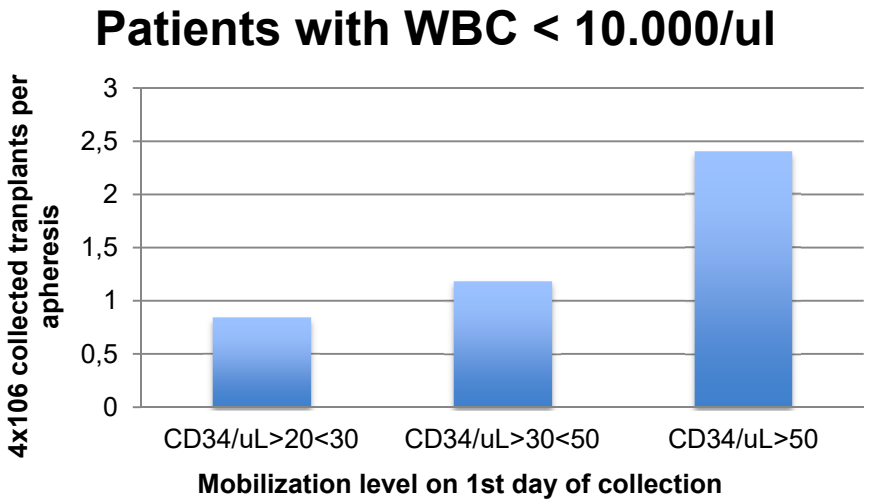
C. Optimal timing

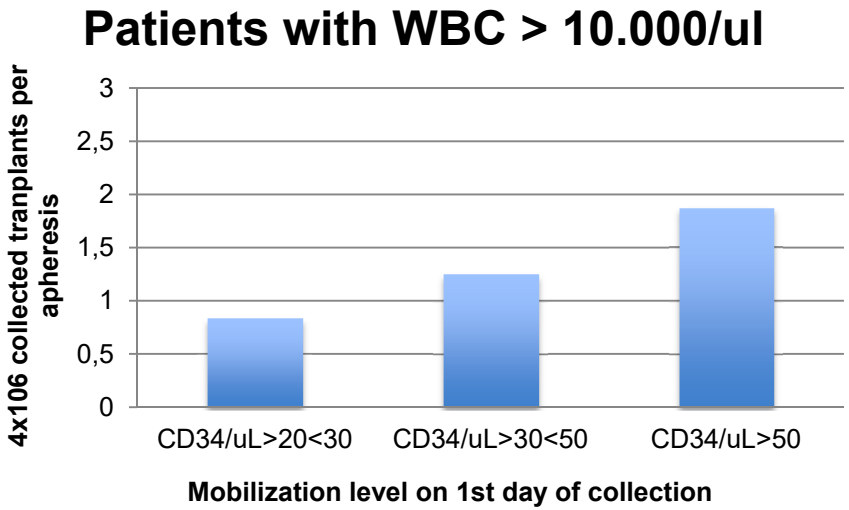
D. Tailoring of blood volume processing

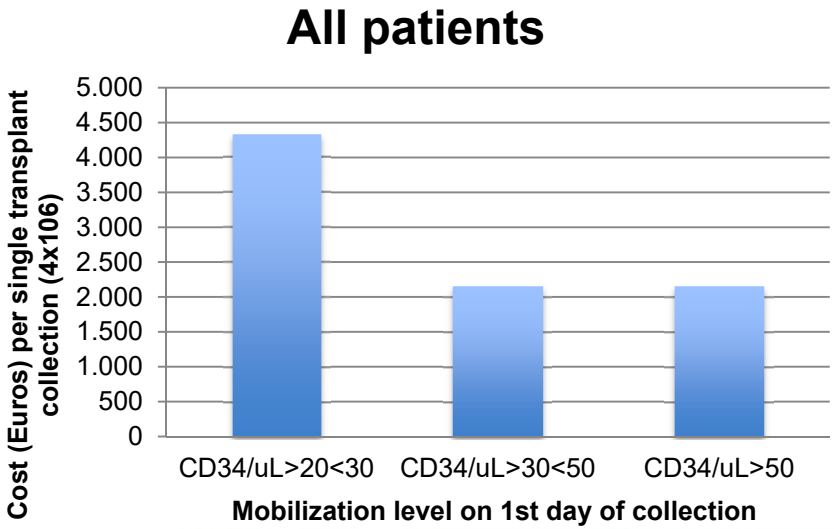
E. Selectivity versus efficiency

Optimal timing

Contributo di una singola aferesi alla raccolta del Tx – Costi della raccolta del singolo Tx



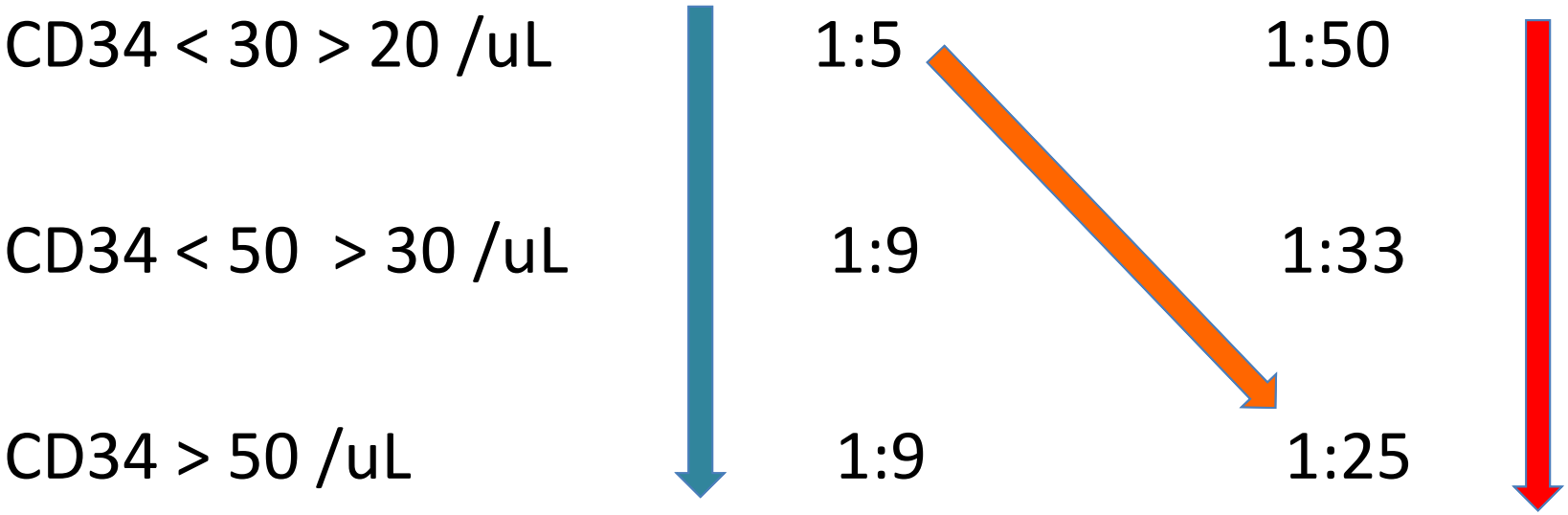




Dati non pubblicati derivanti da esperienza personale e adattati da:
Pierelli L et al. Vox Sanguinis 2006;91:126-134

Qualita' del prodotto di raccolta

rapporto tra CD34 e Gran raccolti



Tailoring of blood volume processing

Vox Sanguinis (2006) **91**, 126–134

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ORIGINAL PAPER

Accurate prediction of autologous stem cell apheresis yields using a double variable-dependent method assures systematic efficiency control of continuous flow collection procedures

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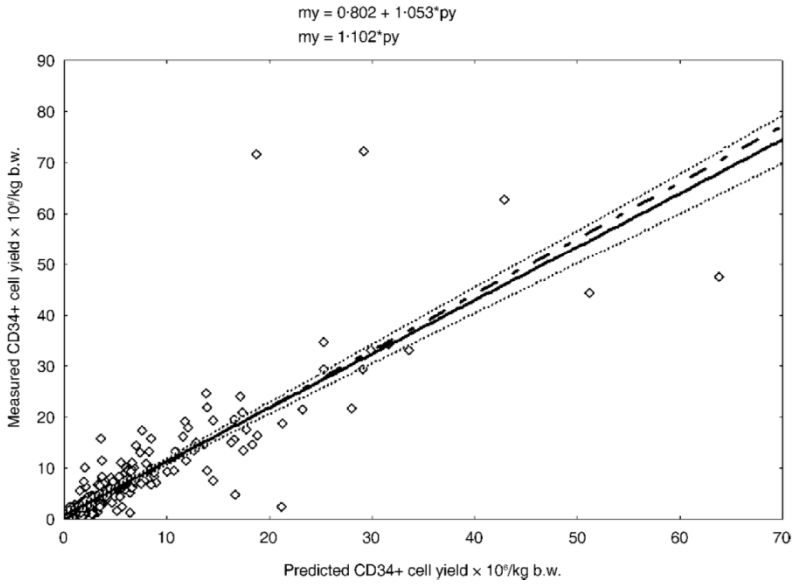


Fig. 2 Standard regression and zero-point regression analysis generated by matching measured and predicted yields obtained by formula (b). Data relative to 313 AHSC collections by leukaphereses have been plotted in a regression graph where standard regression equation (dashed line on the graph) and zero-point regression (solid line on the graph) equations have been shown (my, measured yields; py, predicted yields; confidence intervals are shown as dotted lines).

The predictive formula is simple, works independently by the weight and may be resolved to predict also the volume to be processed for a given CD34 cell dose target

A. CD34 cell precount (10^6 / l)

B. CD34 cell yield prediction or CD34 cell dose target (10^6 /Kg)

C. Blood volume processed (l/kg)

D. Collection efficiency expressed in the 0-1 interval (eg 50 %= 0.5)

Predictive formula	B (Predicted CD34x10^6 /Kg)= A*C*D
Tailoring of blood volume to be processed	C (Blood volume to be processed l/kg= B/(A*D)

Examples

PREDICTION OF YIELD :

A= 70

C= 0.22 l/kg

D= 0.5

→ predicted CD34x10^6/kg (B)= AxCxD=70x0.22x0.5 = 7.7

PREDICTION OF VOLUME TO BE PROCESSED FOR A GIVEN TARGET:

A= 70

D= 0.5

B= 7.7

→ predicted blood volume to be processed l/kg (C)=

B/(AxD) = 7.7/(70x0,5) = 0.22 (ie 220 ml/kg)

Results after tailoring collection for blood volume to be processed on the basis of CD34 precount by our formula

Difference between the volume to be processed using a standard 200 ml / kg vs volume tailoring by our formula:

All procedures -3.956 ml (reaching the target in 74% of cases)

Single procedure -5.218 ml (reaching the target in 94% of cases)

Two procedures -2.799 ml (reaching the target in 58% of cases)

More than 2 procedures 2.194 ml (reaching the target in 50% of cases)

Efficiency vs Selectivity

	WBC precount/ul	CD34 precount/ul	Neut %	BV processed lt	WBC count in the harvest/ul	CD34 count in the harvest/ul
Selective PBSC-Lym Program (43)	17,340+/-17,760	124.2+/-115.0	64+/-21	10.86+/-2.82	**161,793+/-217,444**	3,334+/-3,579
Efficient MNC Program (373)	23,720+/-13,420	106.9+/-109.1	73+/-35	11.23+/-4,98	**287,632+/-200,666**	3,349+/4,446

Efficiency vs Selectivity

	Harvest volume ml	NC x10^9 in the harvest	MNC x10^9 in the harvest	CD34 x10^6 in the harvest	NC x10^9 /kg in the harvest	CD34 x10^6 /kg in the harvest
Selective PBSC-Lym Program (43)	212.3+/-74.7	26.57+/-24.03	12.86+/-8.16	570.87+/-472.11	0.379+/-0.346	7.76+/-5.87
Efficient MNC Program (373)	210.9+/-72.0	57.29+/-28.28	16.53+/-13.43	557.38+/-542.83	0.797+/-0.409	7.69+/7.70

Efficiency vs Selectivity

	Hct % of the harvest	PLT /ul in the harvest	CD34 collection efficiency %
Selective PBSC-Lym Program (43)	6.23+/-3.96	737,964+/-949,705	61.36+/-21.11
Efficient MNC Program (373)	11.08+/-12.31	910,948+/-817,745	66.55+/-21.64

NC collected per bag during PBSC harvesting

CD34/Kg and NC in several cooperating Italian centers

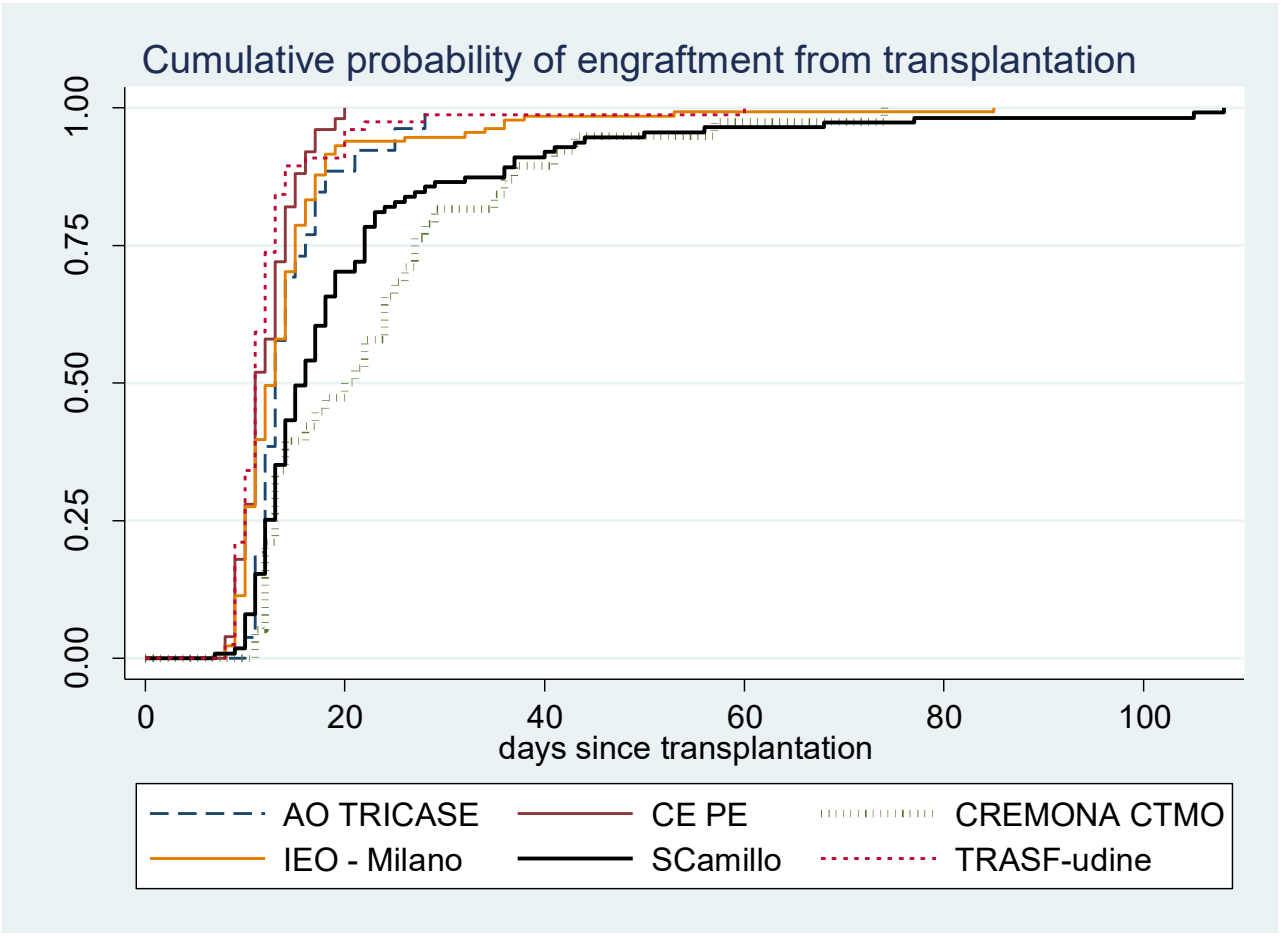
Center	N	Mean	SD	Median	25° pct	75° pct	min	max
NC x 10^9								
AO TRICASE	26	6.7	5.3	4.3	2.8	8.9	2.1	22.4
CE PE	50	13.8	5.0	13.1	10.2	17.3	5.0	23.5
CREMONA CTMO	37	13.9	9.6	12.3	9.3	14.7	1.4	61.5
IEO – Milano	131	26.1	15.6	23.7	14.5	33.3	4.3	98.0
AO San Camillo	111	27.2	11.0	23.9	19.0	35.0	9.6	64.0
TRASF-udine	76	5.8	1.8	5.9	4.8	7.0	1.6	10.6
Total	**431**	**19.1**	**13.9**	**15.7**	**7.9**	**26.0**	**1.4**	**98.0**

NC collected per bag during PBSC harvesting

CD34/Kg and NC in several cooperating Italian centers

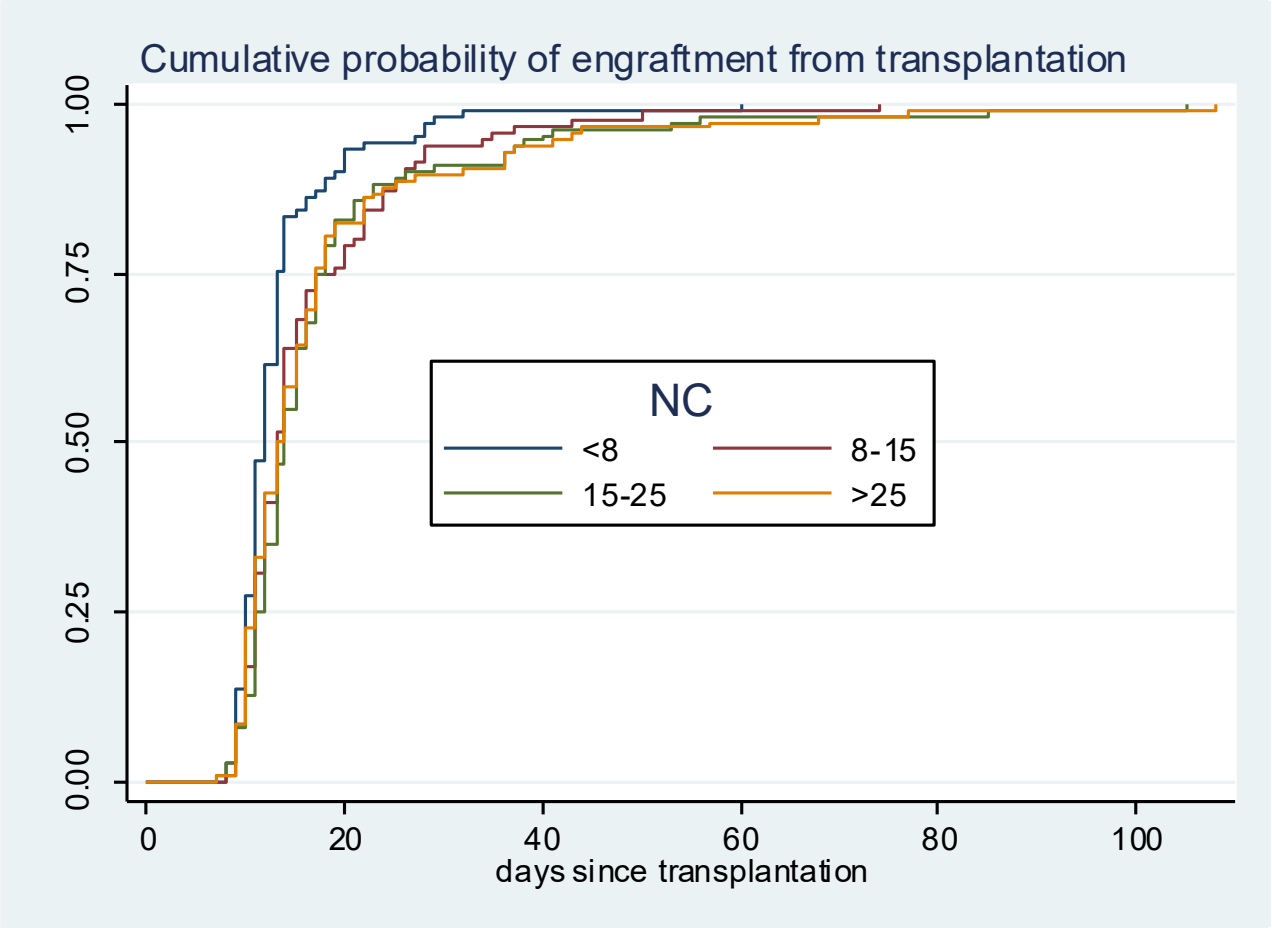
Center	Min	Max	N	Mean	SD	Median	25°pct	75°pct
CD34x10^6/kg								
AO TRICASE	26	2.1	0.9	2.0	1.5	2.3	0.8	5.4
CE PE	50	3.5	2.1	3.1	2.0	5.2	0.5	8.7
CREMONA CTMO	37	4.3	3.3	3.2	2.3	4.7	1.2	14.6
IEO – Milano	131	4.3	3.1	3.1	2.1	5.0	0.3	15.3
AO San Camillo	111	6.2	2.7	5.3	4.6	6.8	2.5	19.6
TRASF-udine	76	2.2	1.9	1.8	1.2	2.6	0.3	14.1
Totale	**431**	**4.2**	**3.0**	**3.5**	**2.1**	**5.3**	**0.3**	**19.6**

Plt engraftment by center



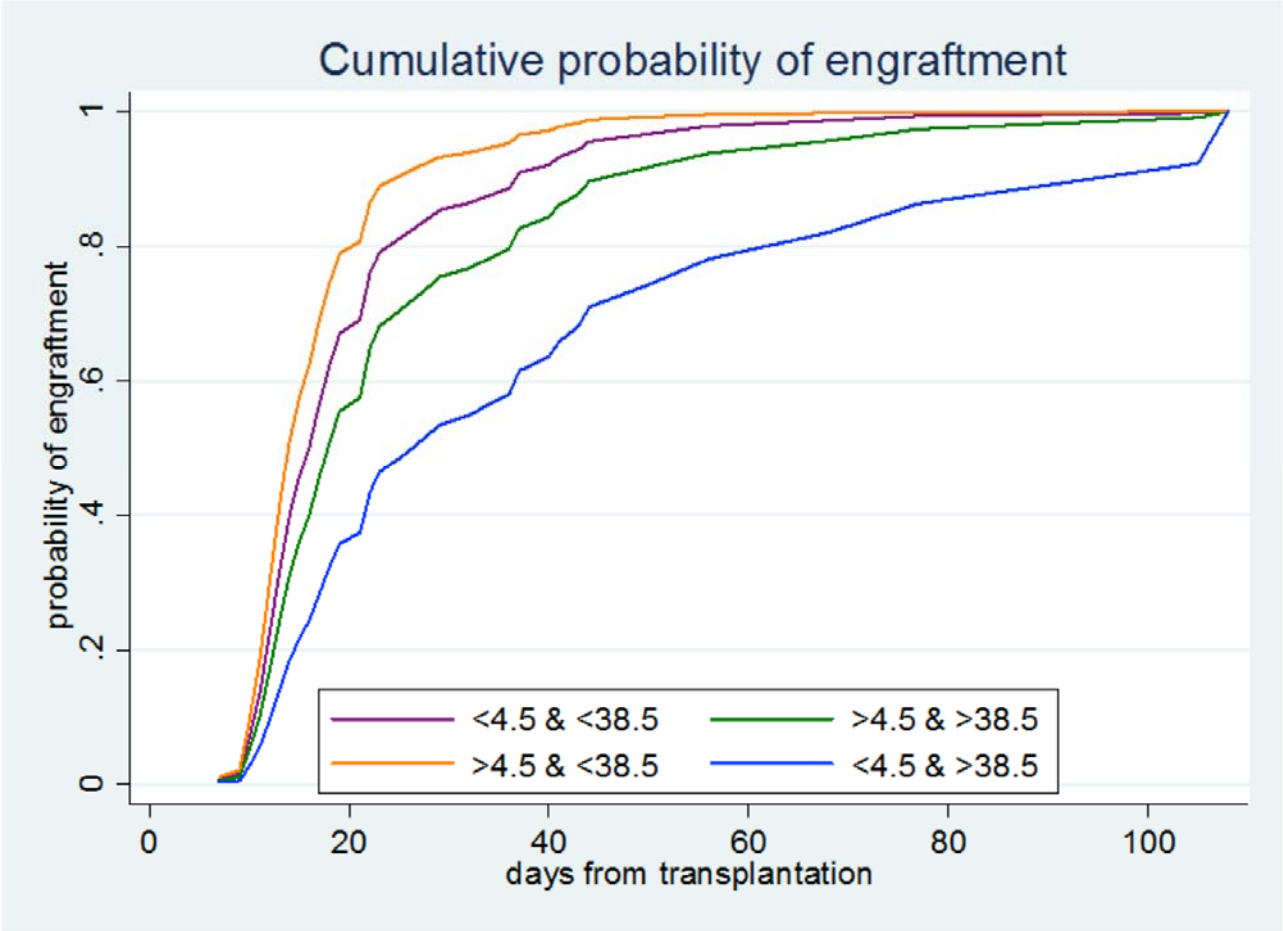
Log-rank test for equality of survivor functions
Pr>chi2 <0.0001

Plt engraftment by total NC infused



Log-rank test for equality of survivor functions
Pr>chi2 = 0.0001

Plt engraftment by combining CD34x10^6/kg and total NC infused (x10^9)(San Camillo Hospital series)



Log-rank test for equality of survivor functions
Pr>chi2 = 0.0115

Study design and population

Retrospective study (2009-2012) involving 8 transplatation units in Italy and 762 patients.
All units were provided by a standardized collection form where to input graft and engraftment data

Transplantation Units	N	%
Milano - IEO	150	19.7
Roma - PTV	145	19.0
Pescara	123	16.1
Roma - San Camillo	115	15.1
Palermo – La Maddalena	87	11.4
Udine	75	9.8
Cremona	40	5.2
Tricase	27	3.5

Results: patient characteristics

	N°	%
Female	343	45
Male	419	55
Median age at transplantation (IQR*)	55.2	(45.0 - 62.6)
Median weight (IQR*)	72.0	(64.0 - 84.0)
Diagnosis		
Multiple Myeloma (MM)	377	49.5
Non Hodgkin Lymphoma (NHL)	248	32.5
Hodgkin disease (HD)	85	11.2
Acute Myeloid Leukemia (AML)	30	3.9
Other diseases (solid tumours, autoimmune diseases)	22	2.9
Plerixafor use		
yes	67	8.8
no	695	91.2

*IQR: Interquartile range

Results: dose and TNC infused

	Median	IQR*		Lowest	Highest
CD34+ per 10^6/Kg	4.46	2.42	6.50	0.20	19.60
Total nucleated cells per 10^9	25.13	14.94	43.95	1.43	317.32
Total nucleated cells per 10^9/Kg	0.35	0.21	0.60	0.03	4.14
Total nucleated cells per 10^9/bag	15.29	9.12	23.12	1.43	146.30
Total nucleated cells per 10^9/bag/Kg	0.21	0.13	0.33	0.02	1.66
Bags infused	2	1	3	1	12
**IQR: Interquartile range*					

Multiple Cox regression model platelet engraftment

		HR	95% CI		p-value
Bag dose	<2.5	1.00			
($CD34^+x10^6$/kg)	2.5-4.5	1.17	0.91	1.49	0.22
	>4.5	1.55	1.17	2.05	0.00
CD34 Dose/TNC/KG	<10	1.00			
	>10	1.35	1.08	1.68	0.01
Age	<60	1.00			
	>60	1.27	1.08	1.50	0.00
Diagnosis	MM or NHL	1.00			
	HD	1.36	1.06	1.73	0.01
	AML	0.65	0.44	0.96	0.03
	Other	1.31	0.84	2.04	0.23

Score contribution platelet engraftment

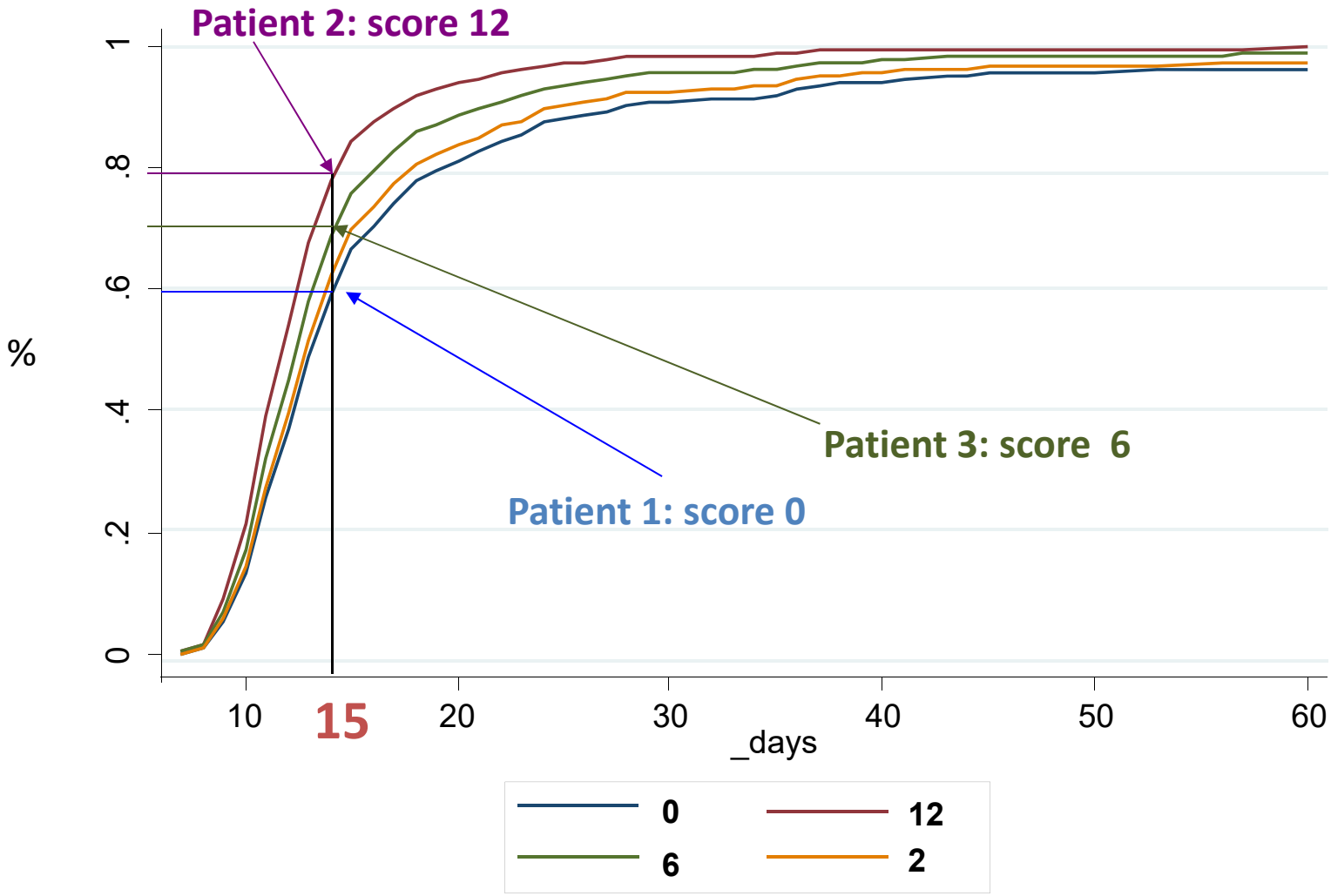
		Score contribution
Bag dose	<2.5	0
($CD34^+x10^6$/kg)		
	2.5-4.5	1
	>4.5	3
CD34 Dose/TNC/KG	<10	0
	>10	2
Age	<60	0
	>60	2
Diagnosis	MM or NHL	3
	HD	5
	AML	0
	Other	5

Patient 1
AML, aged 55 years, received <2.5, and had a dose/TNC ratio <10
Total score 0+0+0+0=0

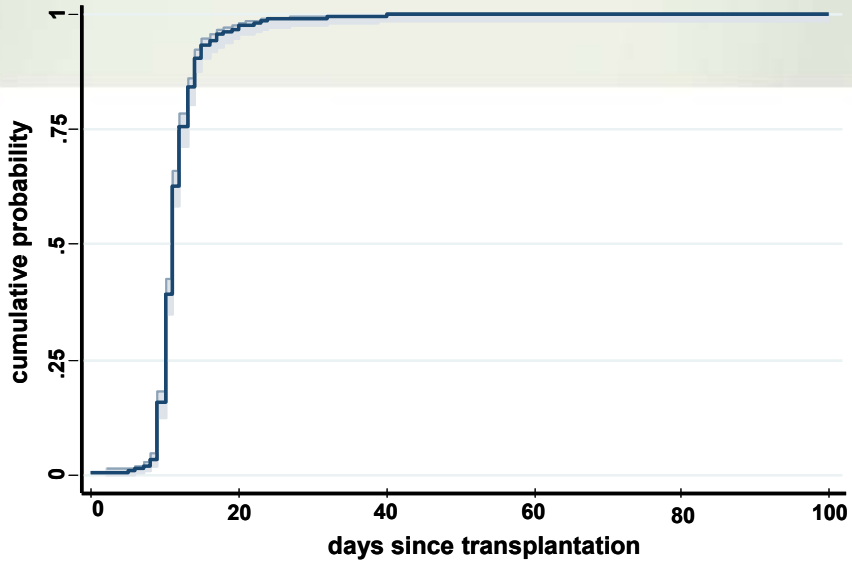
Patient 2
HD, aged 65, received >4.5 and had a dose/TNC ratio >10
Total score 3+2+2+5=12

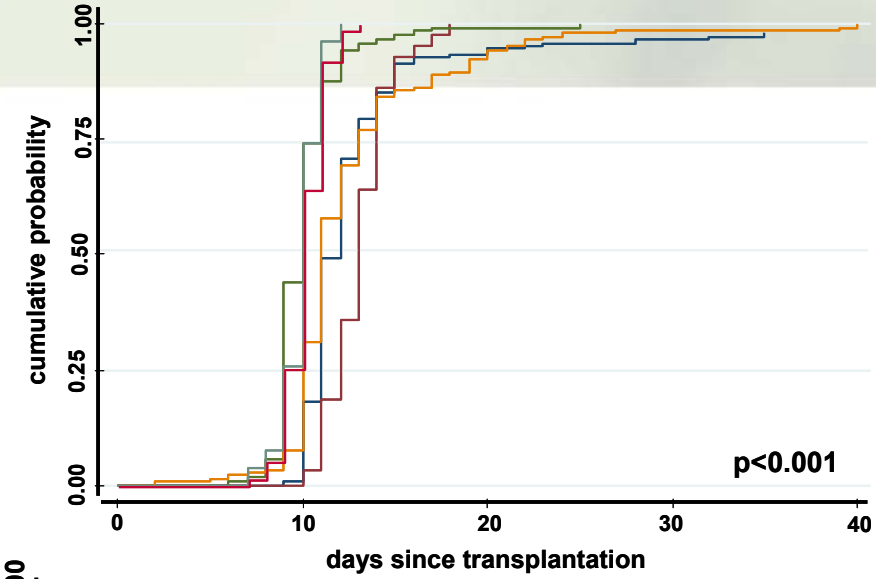
Patient 3
NHL, aged 45, received >4.5 and had a dose/TNC ratio >10
Total score: 3+0+3+0=6

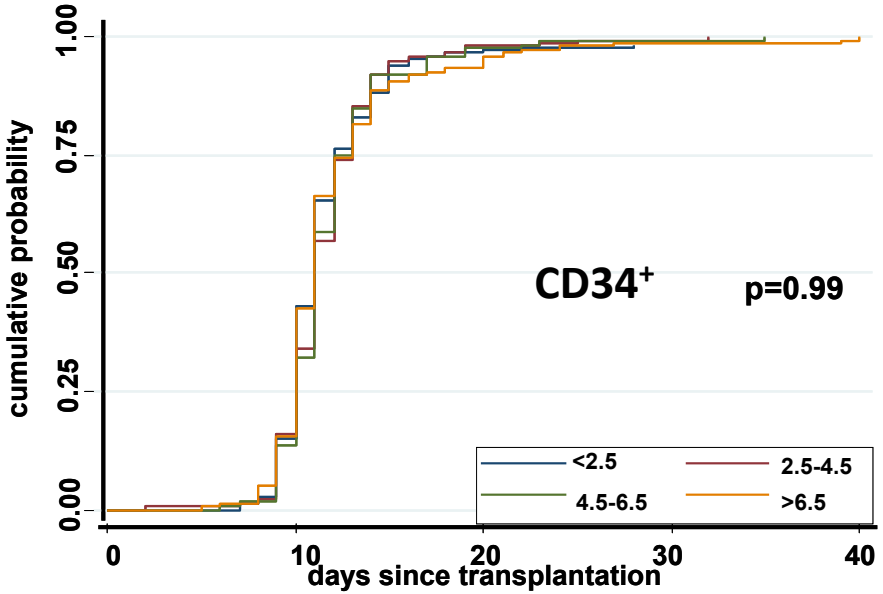
Probability of platelet engraftment by score

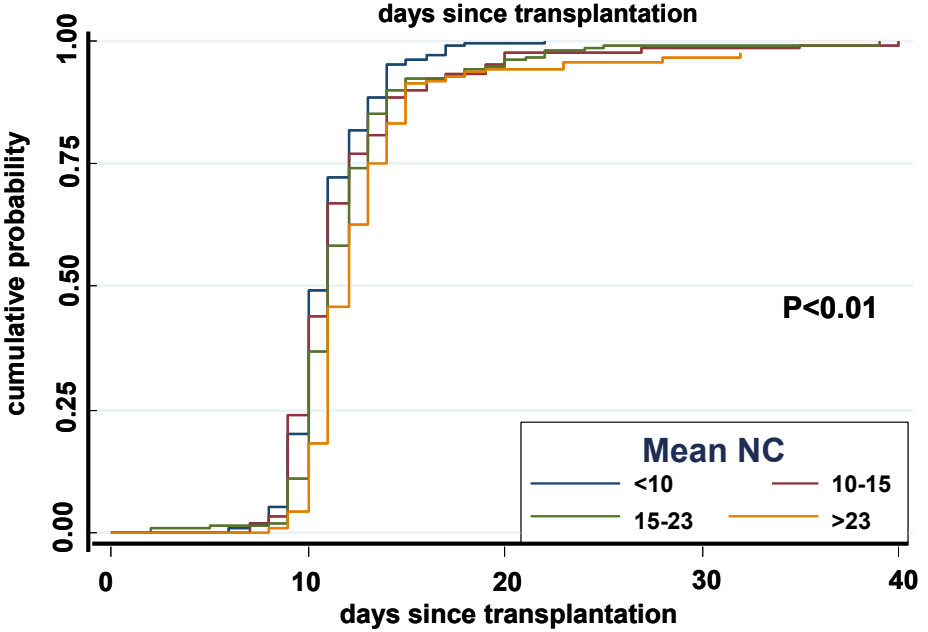


Results: cumulative probability of neutrophil engraftment









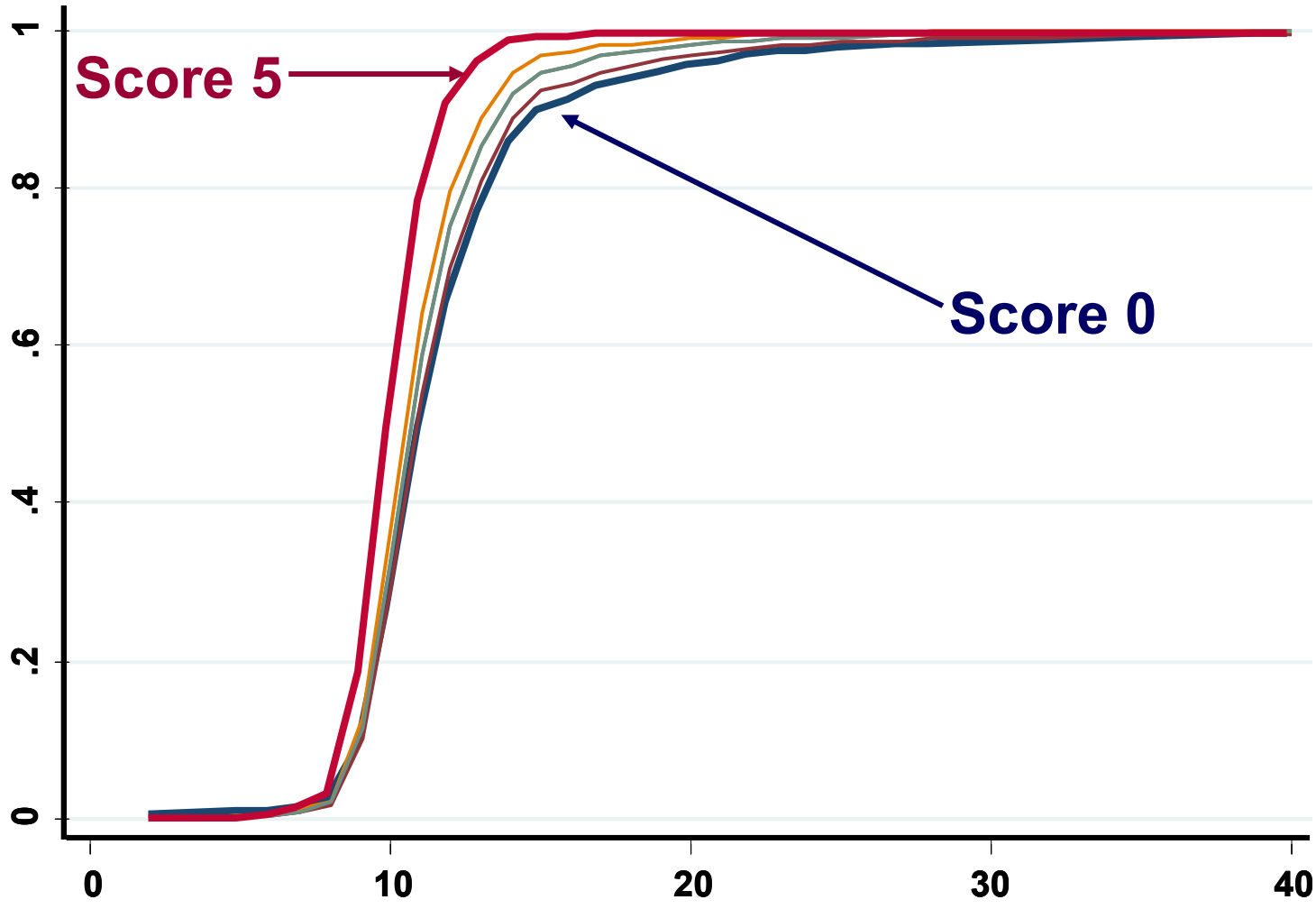
neutrophil engraftment multiple Cox regression model

		HR	95 % CI		p-value
Bag dose	***<2.5***	1.00			
	2.5-4.5	1.15	0.89	1.49	0.29
	>4.5	1.35	1.00	1.82	0.05
Dose/TNC/KG	***<10***	1.00			
	>10	1.46	1.13	1.89	0.00

Score contribution neutrophil engraftment

		Score contribution
Bag dose	<2.5	0
	2.5-4.5	1
	>4.5	2
Dose/TNC/KG	<10	0
	>10	3

Probability of neutrophil engraftment by score



Apheresis Technique - Conclusions

A. New apheretic platforms assure automation, standardization of the HPC-Aph product, small extracorporeal volumes and high component collection efficiency

B. Tailoring of collection procedures by predictive algorythms, with optimization of blood volume processing, reduce donors' discomfort, procedure length, costs and the global volume of storage for the autologous setting

C. Selectivity during collection must be considered as an additional requisite, showing a possible influence on PLT engraftment for frozen/thawed products

Results: dose and TNC infused

	Median	IQR*		Lowest	Highest
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Total nucleated cells per 10^9	25.13	14.94	43.95	1.43	317.32
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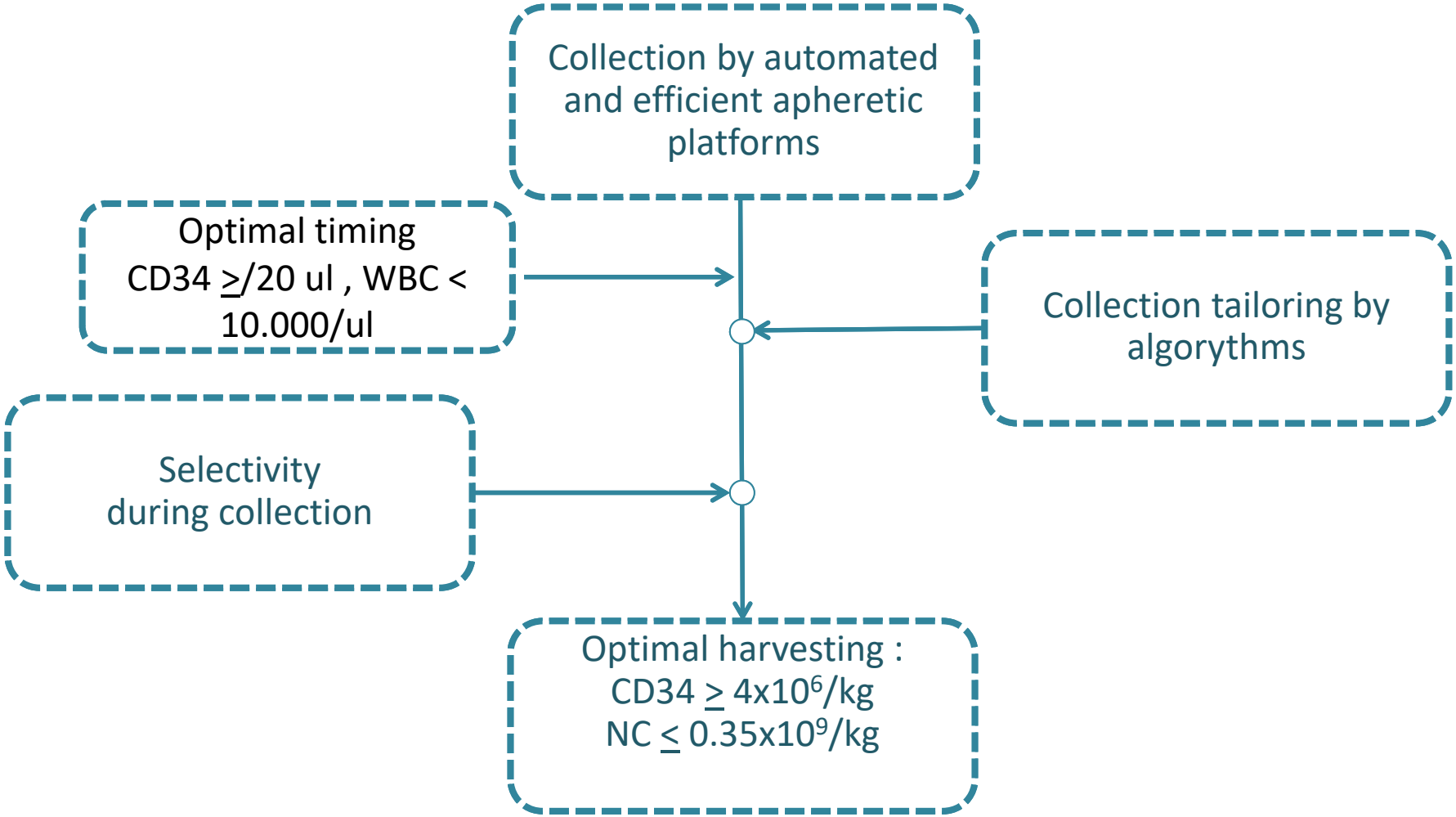
Bags infused	2	1	3	1	12
**IQR: Interquartile range*					

median days to achieve engraftment :
11 (2-100) and 13 (7-108) for granulocyte and PLT, respectively

Apheresis Technique - Conclusions



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Grazie a voi per l’attenzione !