UNIVERSITÀ DEGLI STUDI DI PADOVA

DIVISIONE E CATTEDRA DI CHIRURGIA TORACICA E
CENTRO TRAPIANTO DI POLMONE

FEDERICO REA

Qual è il presente e il futuro per il trapianto di polmone «marginale»?

STATI GENERALI
20 ANNI 1999·2019
RETE NAZIONALE TRAPIANTI

6·7·8 NOVEMBRE
ROMA

DONATORI CON CRITERI ESTESI

- *Extended criteria*
  - **Età > 55 anni** } NON MODIFICABILI
  - **Storia di fumo > 20 pack-year**
  - **PaO2 < 300 mmHg con FiO2 = 1 e PEEP = 5 cmH2O** } MODIFICABILI
  - **Infiltrati alla radiografia del torace**
  - **Secrezioni purulente alla broncoscopia** INTERPRETABILE

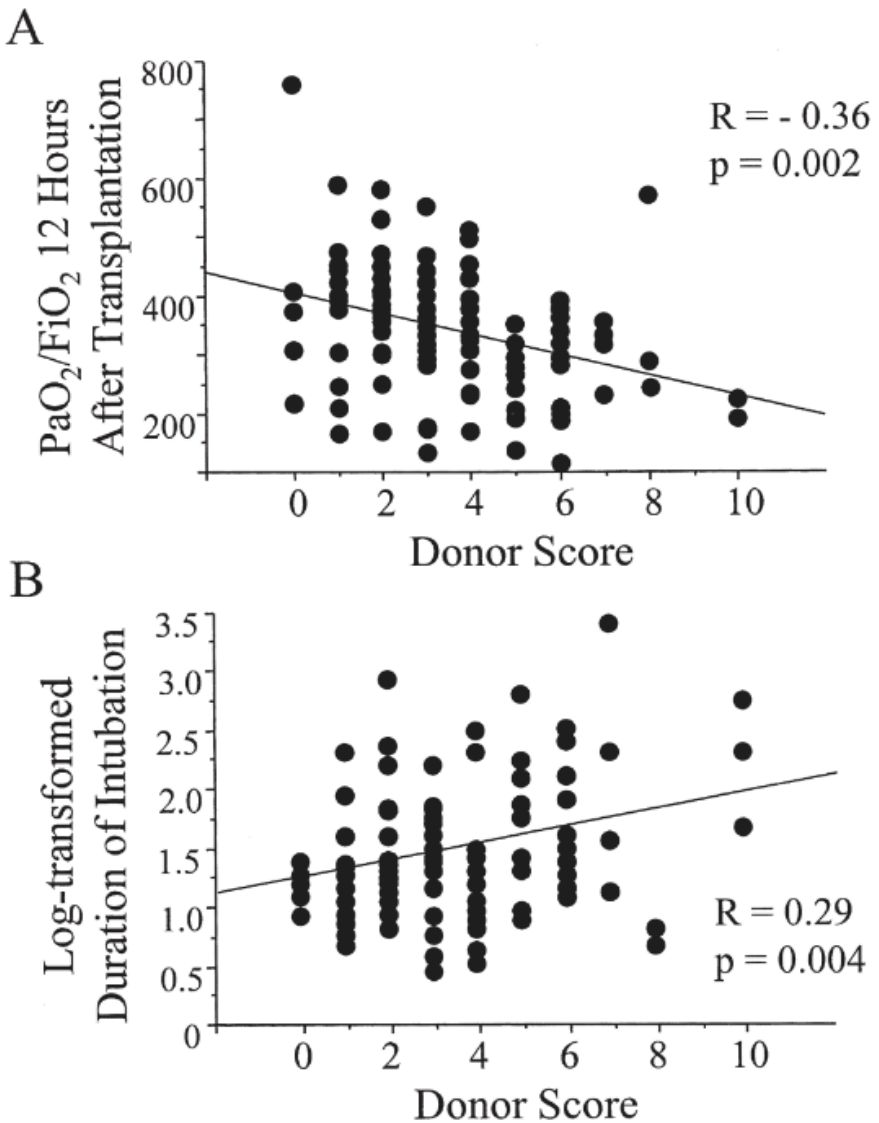
- **La violazione di almeno un criterio avviene in più della metà dei casi, ma numerosi studi hanno fatto chiarezza in merito a limiti e modalità nell'uso di donatori marginali per età, PaO2, Rx e broncoscopia.**

Feasibility and Utility of a Lung Donor Score: Correlation With Early Post-Transplant Outcomes

Takahiro Oto, MD, Bronwyn J. Levvey, RN, Helen Whitford, MD,
Anne P. Griffiths, FRCNA, Tom Kotsimbos, MD,
Trevor J. Williams, MD, and Gregory I. Snell, MD

Donor Scoring Criteria

Category	Stratification	Score
Age (years):	< 45	0
	45–54	1
	55–59	2
	≥ 60	3
Smoking history (pack-years):	< 20	0
	20–39	1
	40–59	2
	≥ 60	3
Chest X-ray:	Clear	0
	Minor	1
	Opacity ≤ 1 lobe	2
	Opacity > 1 lobe	3
Secretions:	None	0
	Minor	1
	Moderate	2
	Major	3
Pao_2/Fio_2:	> 450	0
	351–450	2
	301–350	4
	≤ 300	6



COME PUO' CAMBIARE L'OTO SCORE

T0: POMERIGGIO

T1: SERA

T2: PRELIEVO

CALCOLO DEL PUNTEGGIO OTO SCORE PER IL TRAPIANTO DI POLMONE

Donatore	Serino Antonietta
Ospedale	ospedale del mare Napoli
Codice TrapNet	312473
Codice SIT	N.
Data segnalazione	31/10/19

	T0	T1	T2	T3
data:	data	data	data	data
ora:	ora	ora	ora	ora
Età (anni)	**55-59**	**55-59**	**55-59**	**-**
Fumo (pack-years)	**<20**	**<20**	**<20**	**-**
Chest X-ray	**Clear**	**Clear**	**Clear**	**-**
Secrezioni	**Moderate**	**Moderate**	**Minor**	**-**
Pao2/Fio2	**351-450**	**<301**	**>450**	**-**
OTO SCORE	**6**	**10**	**3**	**-**

Oto T, Levvey BJ, Whitford H, Griffiths AP, Kotsimbos T, Williams TJ, Snell GI. Feasibility and utility of a lung donor score: correlation with early post-trasplant outcomes. Ann Thorac Surg. 2007 Jan; 83 (1): 257-63

Interactive CardioVascular and Thoracic Surgery 14 (2012) 183–187

Does the use of extended criteria donors influence early and long-term results of lung transplantation?

Marco Schiavon, Pierre-Emmanuel Falcoz*, Nicola Santelmo and Gilbert Massard

Open Questions:

- Marginal donor and morbidity - mortality ?
- Marginal donor and survival ?
- Which marginal criteria ?

DONATORI CON CRITERI ESTESI ED EARLY OUTCOMES: UN DIBATTITO ACCESSO

10 STUDI ANALIZZATI

6 study: no significant difference in terms of morbidity and mortality between standard donor and marginal donor

- Mortality at 30 or 60 day
- Primary graft failure
- Length of stay in ICU
- Duration of mechanical ventilation
- Use of CEC
- Lung function (spirometry)

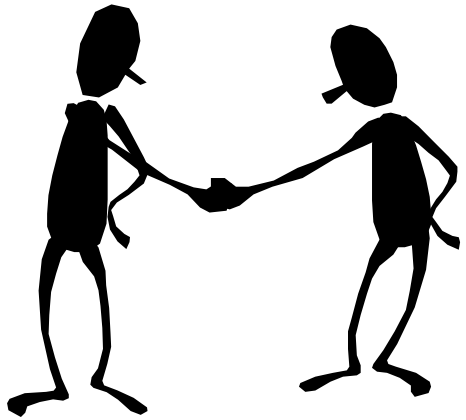
4 study: significant difference in terms of morbidity and mortality between standard donor and marginal donor

- Mortality at 30 or 60 day
- Primary graft failure
- Length of stay in ICU
- Duration of mechanical ventilation
- Lung function (spirometry)

DONATORI CON RITERI ESTESI E SOPRAVVIVENZA: UN CONSENSO GENERALE

10 STUDI ANALIZZATI

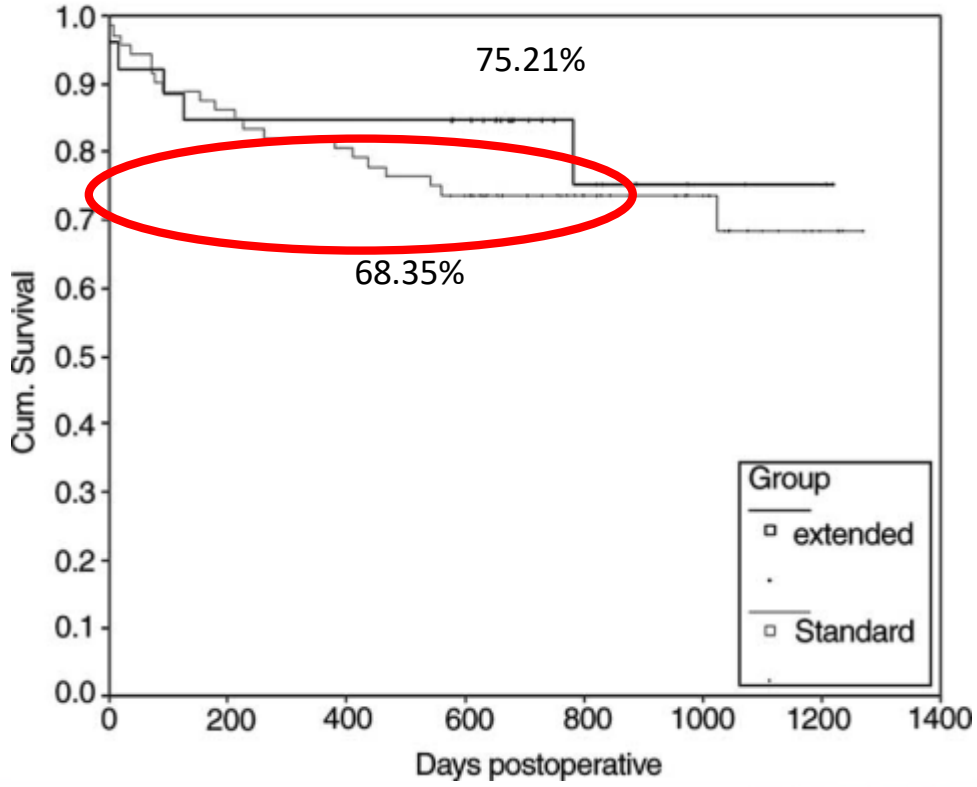
No significant difference in terms of survival (1 year and more) between SD and MD



ELSEVIER
European Journal of Cardio-thoracic Surgery 27 (2005) 757-761
www.elsevier.com/locate/ejcts

Extended donor criteria for lung transplantation—a clinical reality☆

Clemens Aigner[a], Guenther Winkler[a], Peter Jaksch[a], Gernot Seebacher[a], Gyorgy Lang[b], Sharokh Taghavi[a], Wilfried Wisser[a], Walter Klepetko[a,*]



2005

FATTORI INDIVIDUALI DI MARGINALITA’

- Età ≥ 55 anni
- PaO_2 < 300 mmHg ; FiO_2 = 1.0 ; PEEP + 5 cm H_2O
- Abitudine tabagica (fumatore / non fumatore)
- Broncoscopia (secrezioni purulente / non purulente)

ELSEVIER

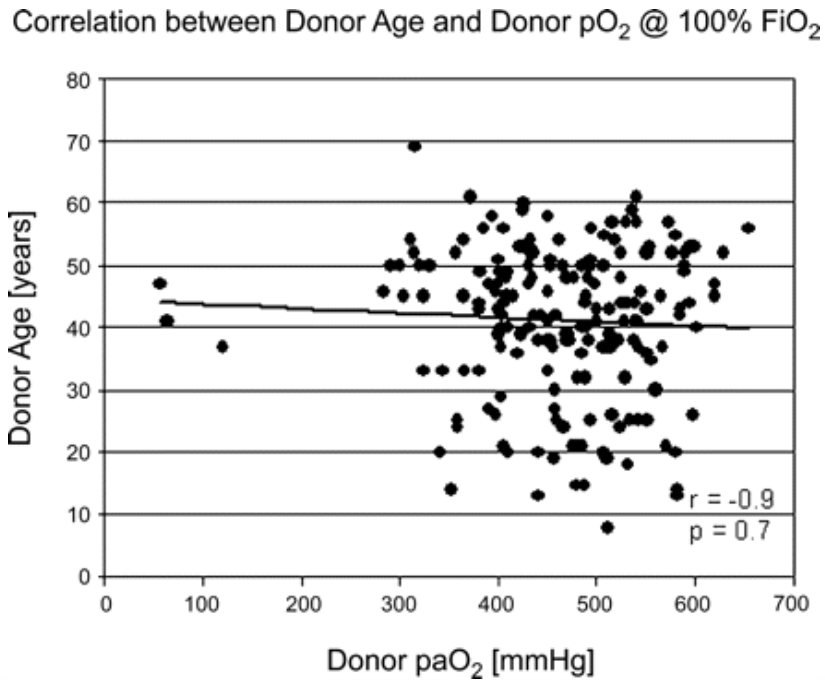
European Journal of Cardio-thoracic Surgery 38 (2010) 192–197

www.elsevier.com/locate/ejcts

Lung transplantation using donors 55 years and older: is it safe or just a way out of organ shortage?☆

Nikolaus Pizanis *, Jens Heckmann, Konstantinos Tsagakis, Paschalis Tossios, Parwis Massoudy, Daniel Wendt, Heinz Jakob, Markus Kamler

Conclusions. **No significant differences in early, intermediate and long-term outcomes. Spirometric function: trend toward a lower percentage from 36 months PO in the MD group.**

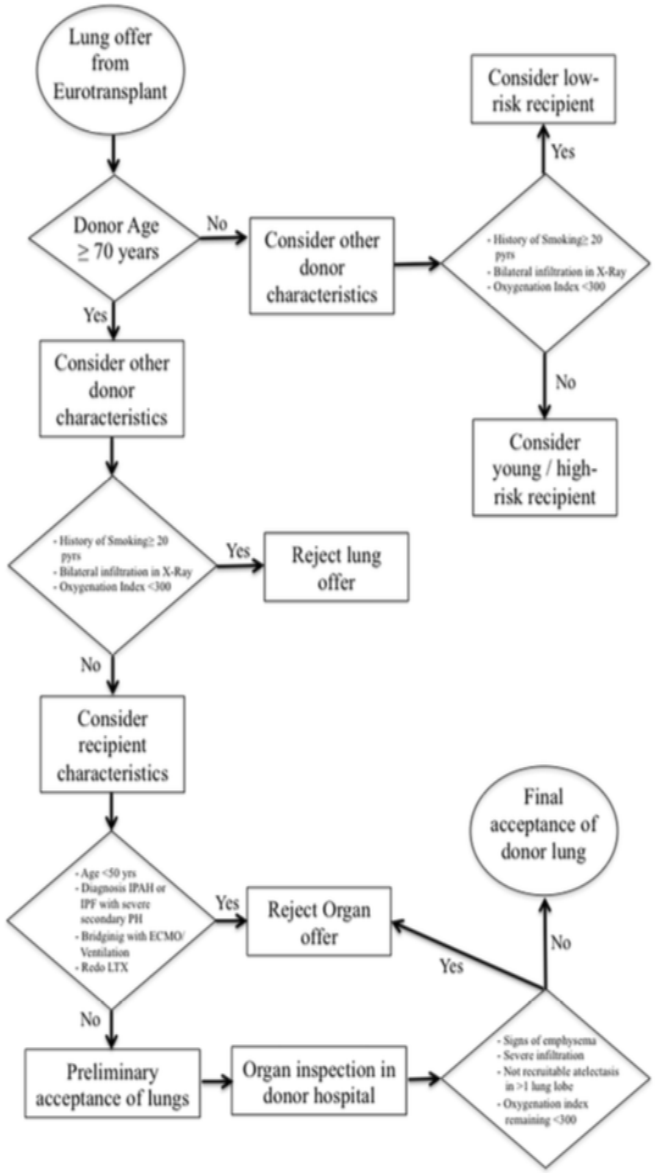


J Heart Lung Transplant 2015;34:1325–1333

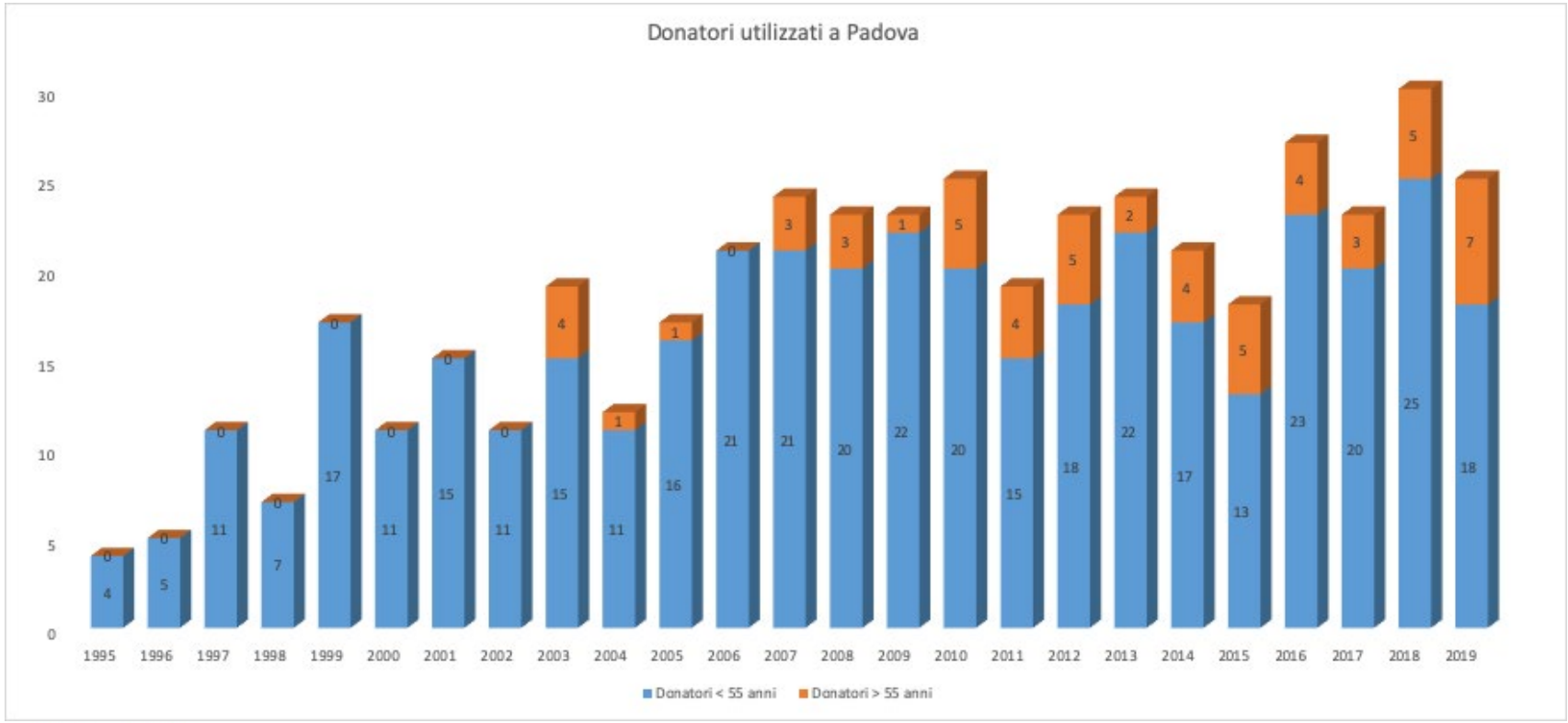
Survival and spirometry outcomes after lung transplantation from donors aged 70 years and older

Wiebke Sommer, MD,[a,1] Fabio Ius, MD,[a] Jawad Salman, MD,[a] Murat Avsar, MD,[a] Igor Tudorache, MD,[a] Christian Kühn, MD,[a] Bettina Wiegmann, MD,[a] Georg Marsch, MD,[a] Tim Kaufeld, MD,[a] Norman Zinne, MD,[a] Thomas Fuehner, MD,[b] Mark Greer, MD,[b] Jens Gottlieb, MD,[b,1] Dietmar Boethig, MD,[c] Axel Haverich, MD,[a,1] Tobias Welte, MD,[b,1] and Gregor Warnecke, MD[a,1]

CONCLUSION: Use of donor lungs aged ≥70 years for transplantation is safe, without compromising survival. However, spirometry findings after transplantation with donors ≥70 years indicate better functional outcomes in emphysema recipients than in idiopathic pulmonary fibrosis recipients.



ESPERIENZA DI PADOVA CON DONATORI ANZIANI



Media utilizzo: 12%

Media utilizzo 1995-2009: 5%

Media Utilizzo 2010-2019: 25%

LA SITUAZIONE IN ITALIA ED EUROPA

DONATORI UTILIZZATI DI POLMONE 2017-2018

		<18	18-55	>55	totale
POLMONE	**2017**	11	104	28	**143**
POLMONE	**2018**	5	99	36	**140**
	totale	**16**	**203**	**64**	**283**

*Donors from Spanish hospitals		Donor* age 0-55	> 55	Total
AÑODON	2009	157 72%	62 28%	**219**
	2010	179 74%	65 26%	**244**
	2011	169 69%	77 31%	**246**
	2012	172 65%	92 35%	**264**
	2013	212 67%	105 33%	**317**
	2014	162 55%	133 45%	**295**
	2015	214 63%	127 37%	**341**
	2016	186 55%	154 45%	**340**
	2017	224 54%	191 46%	**415**
	2018	211 47%	237 53%	**448**
	Total	**1886 60%**	**1243 40%**	**3129**

	DBD		DCD	
Donation year	**Number of lung donors**	**Number (%) lung donors aged 56 years or over**	**Number of lung donors**	**Number (%) lung donors aged 56 years or over**
2009	150	20 (13)	16	2 (13)
2010	152	17 (11)	24	2 (8)
2011	181	31 (17)	23	2 (9)
2012	164	38 (23)	35	7 (20)
2013	189	33 (17)	43	12 (28)
2014	171	35 (20)	41	10 (24)
2015	163	34 (21)	48	11 (23)
2016	151	35 (23)	26	5 (19)
2017	170	38 (22)	43	7 (16)
2018	169	41 (24)	50	14 (28)

Organe prélevé et greffé	Age en classe et moyenne	2013 (N)	2014 (N)	2015 (N)	2016 (N)	2017 (N)	2018 (N)
Poumon	0 - 17 ans	20	16	14	8	15	21
	18 - 49 ans	140	145	155	176	162	153
	50 - 64 ans	107	124	132	125	136	129
	65 ans et plus	32	37	37	50	49	55
	Moyenne [IC 95%]	46,4 [44,6 - 48,2]	46,9 [45,2 - 48,6]	47,5 [45,8 - 49,1]	48,1 [46,6 - 49,6]	47,9 [46,3 - 49,5]	47,6 [45,9 - 49,4]

Comparison of Outcomes From Smoking and Nonsmoking Donors: Thirteen-Year Experience

Marius Berman, MD, Kim Goldsmith, MS, MPH, David Jenkins, MS, FRCS, Catherine Sudarshan, FRCS, Pedro Catarino, FRCS, Nair Sukumaran, FRCS, John Dunning, FRCS, Linda D. Sharples, PhD, Steven Tsui, MD, FRCS, and Jasvir Parmar, PhD, FRCP

Ann Thorac Surg 2010;

2010

Conclusions. **Recipient for smoking donors had higher ICU stay (> 2 d, p=0.004), lower 3 months survival (13 vs 21%, p=0.04), 20% higher risk of MV > 10 d (p=ns).**
No difference in rejection or infection rates

Table 4. Analysis of Variables Associated With ITU Stay

Risk Factor	ITU Below Median (n = 302)	ITU Above Median (n = 143)	Odds Ratio (95% CI)	*p* Value
Donor smoked, n (%)	103 (38)	76 (55)	1.9 (1.3, 2.9)	0.002

Ann Thorac Surg
2013;95:1912–8

Double-Lung Transplantation Can Be Safely Performed Using Donors With Heavy Smoking History

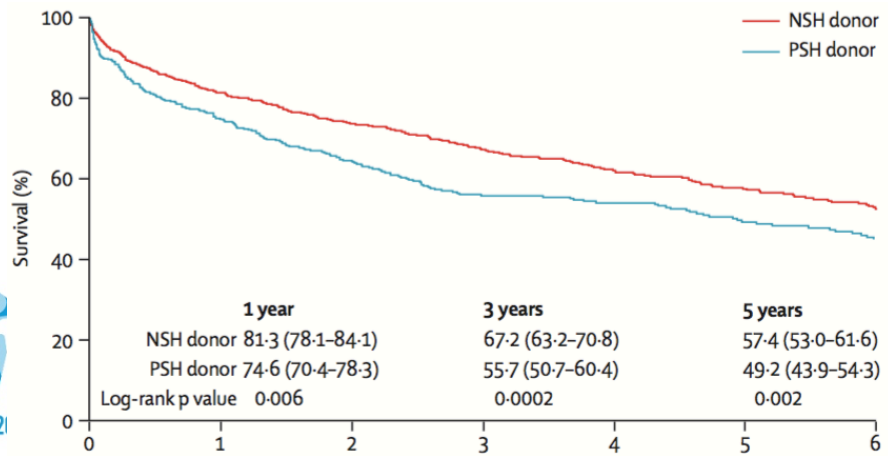
Sharven Taghavi, MD, MPH, Senthil Jayarajan, MD, Eugene Komaroff, PhD, Tetsuya Horai, MD, Stacey Brann, MD, Francis Cordova, MD, Gerard Criner, MD, T. Sloane Guy, MD, MBA, and Yoshiya Toyoda, MD

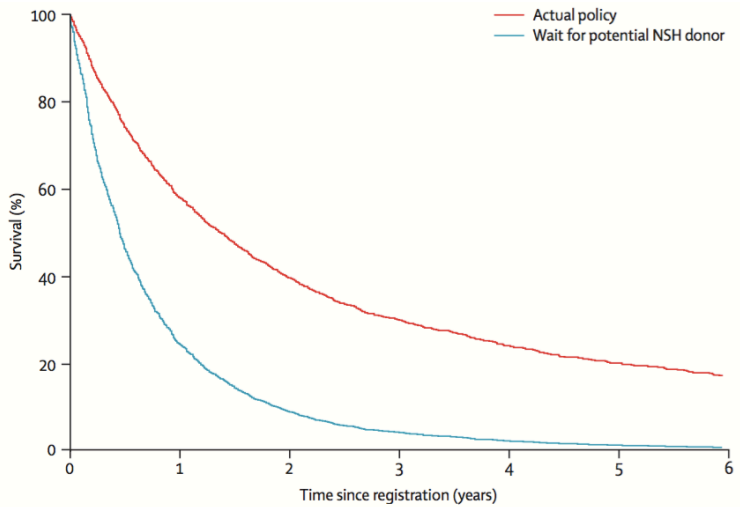
Recipients of lungs from HSDs had longer median length of stay (18.0 vs 17.0 days, $p < 0.001$). Freedom from bronchiolitis obliterans syndrome ($p = 0.09$), decrement in FEV_1 ($p = 0.12$), peak FEV_1 (79.8% vs 79.0%, $p = 0.51$), and median survival (2,043 vs 1,928 days, $p = 0.69$) were not different. On multivariate analysis, HSD lungs were not associated with death (hazard ratio, 1.003; 95% confidence interval, 0.867 to 1.161, $p = 0.96$).

Lancet 2012; 380: 747–55

Effect of donor smoking on survival after lung transplantation: a cohort study of a prospective registry

*Robert S Bonser, Rhiannon Taylor, David Collett, Helen L Thomas, John H Dark, James Neuberger, on behalf of members of the Cardiothoracic Advisory Group to NHS Blood and Transplant and the Association of Lung Transplant Physicians (UK)**





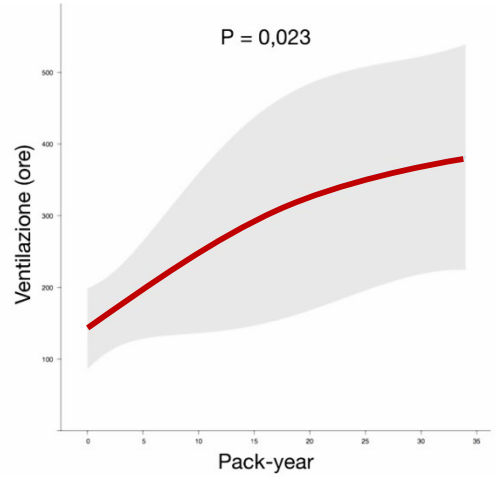
ESPERIENZA DI PADOVA
1995-2015, 355 TRAPIANTI

Obiettivi

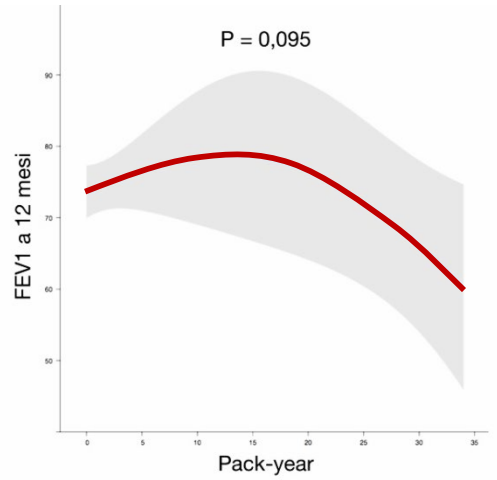
- Studio dell'impatto della storia di fumo del donatore sugli outcome post-trapianto (intubazione, ospedalizzazione, PGD, funzionalità respiratoria, rigetto, sopravvivenza)
- Valutazione delle alterazioni istologiche sul graft in presenza di storia di fumo del donatore

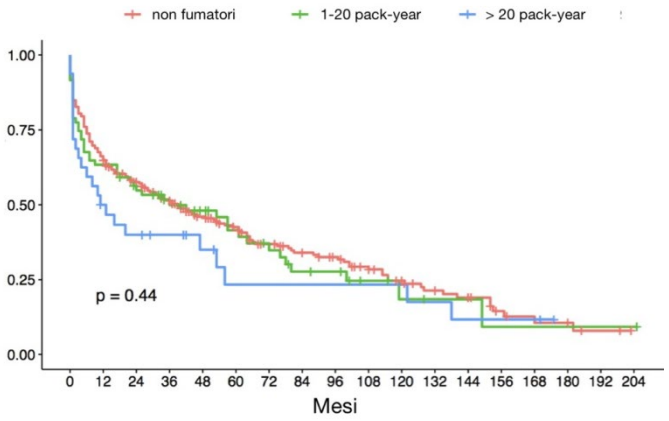
ESPERIENZA DI PADOVA
RISULTATI

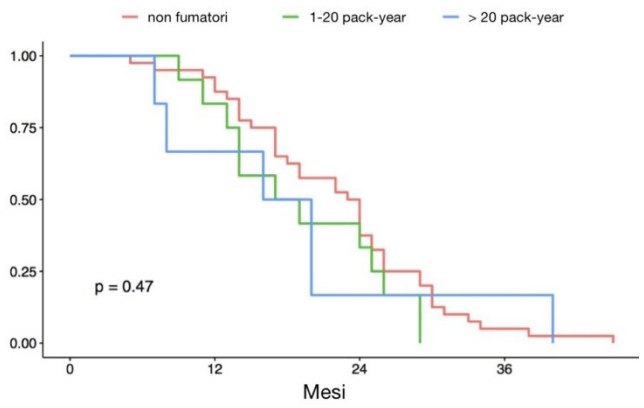
Prolungata ventilazione e ospedalizzazione



Tendenza a riduzione FEV1 a 1 anno







Sopravvivenza (overall e libera da rigetto cronico) non significativamente inferiore

RISULTATI ANALISI PATOLOGICA

Tabella V – Analisi multivariata: danno da ischemia-riperfusione

	Edema		Congestione		Marginazione leucocitaria	
	Effetto (IC95%)	P	Effetto (IC95%)	P	Effetto (IC95%)	P
Fumo	-0,76 (-3,47-1,95)	0,63	-0,07 (-3,27-3,13)	0,12	0,56 (-2,64-3,75)	0,91
Età donatore	0,22 (-0,19-0,62)	0,29	0,16 (-0,32-0,64)	0,51	0,1 (-0,37-0,58)	0,67
Durata intubazione	0 (-0,75-0,76)	0,99	-0,62 (-1,52-0,28)	0,17	-0,75 (-1,65-0,14)	0,10
Tempo di ischemia	0,02 (-0,26-0,3)	0,88	0,02 (-0,31-0,34)	0,92	0,12 (-0,21-0,45)	0,48

Tabella VI – Analisi multivariata: altre lesioni del graft

	Enfisema		Bronchiolite		Antracosi		Flogosi interstiziale	
	Effetto (IC95%)	P	Effetto (IC95%)	P	Effetto (IC95%)	P	Effetto (IC95%)	P
Fumo	0,18 (-2,2-2,57)	0,93	-0,69 (-3,8-2,43)	0,82	0,65 (-2,08-3,39)	0,66	-0,51 (-2,83-1,8)	0,39
Età donatore	0,29 (-0,07-0,65)	0,11	0,05 (-0,42-0,52)	0,83	0,4 (-0,01-0,81)	0,05	0,16 (-0,18-0,5)	0,35
Durata intubazione	-0,09 (-0,76-0,58)	0,79	0,69 (-0,19-1,57)	0,12	0,38 (-0,39-1,15)	0,33	0,44 (-0,21-1,09)	0,18
Tempo di ischemia	0,08 (-0,16-0,32)	0,52	-0,2 (-0,51-0,11)	0,20	0,18 (-0,09-0,46)	0,19	0,04 (-0,2-0,29)	0,73

Marginal donor lungs: A reassessment

Andrew F. Pierre, MD, MSc, FRCSC

The Journal of Thoracic and Cardiovascular Surgery • Volume 123

2002

TABLE 9. Deaths with extended criteria per extended criteria

Criteria	Proportion
Smoking >20 pack-years	2/26 (8%)
Age >55 y	1/9 (11%)
Abnormal chest radiograph	8/41 (20%)
Purulent bronchoscopic findings	3/8 (38%)

ELSEVIER

European Journal of Cardio-thoracic Surgery 27 (2005) 762-767

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

2005

Extended donor lungs: eleven years experience in a consecutive series☆

Didier Lardinois[a], Marc Banysch[a], Stephan Korom[a], Sven Hillinger[a], Valentin Rousson[b], Annette Boehler[c], Rudolf Speich[d], Walter Weder[a,*]

The combination of PaO_2<300 mmHg with purulent secretion at bronchoscopy seemed to influence the early outcome of recipients from extended donor lungs negatively.

Influence of Donor Characteristics on Outcome After Lung Transplantation: A Multicenter Study

Gabriel Thabut, MD,[a] Hervé Mal, MD,[a] Jacques Cerrina, MD,[b] Philippe Dartevelle, MD,[b] Claire Dromer, MD,[c] Jean-François Velly, MD,[c] Marc Stern, MD,[d] Philippe Loirat, MD,[d] Michelle Bertocchi, MD,[e] Jean-François Mornex, MD,[e] Alain Haloun, MD,[f] Philippe Despins, MD,[f] Christophe Pison, MD,[g] Daniel Blin, MD,[g] Gerald Simonneau, MD,[h] and Martine Reynaud-Gaubert MD[i]

The Journal of Heart and Lung Transplantation

2005

Conclusions: **Although liberalization of lung-donor criteria may be considered to overcome the shortage of lung donors, our data suggest that the violation of the gas-exchange criterion should be avoided.**

Table 3. Multivariate Analysis of Factors Associated With Long-Term Survival (Cox model)*

Variable	Hazard ratio	95% CI	*p* Value
Donor age, year (by 10-year increase)	1.03	0.94–1.31	0.55
Donor Pao_2/Fio_2 (continuous, by 100-point increase)	0.90	0.81–0.99	0.04
Donor Pao_2/Fio_2 according to two groups			
≥350	1	. . .	
<350	1.43	1.10–1.85	0.01
Blood group mismatch†	1.30	0.93–1.81	0.13
Donor cause of death			0.78
Traumatic brain injury	1	. . .	
Nontraumatic brain injury (stroke)	1.06	0.85–1.32	
Other (brain anoxia, hanging)	1.11	0.81–1.51	
Donor sex, female	1.45	1.06–1.99	0.02
Recipient sex, female	1.03	0.78–1.36	0.83
Interaction term (donor sex, recipient sex)	0.59	0.37–0.93	0.024

Influence of Donor Characteristics on Outcome After Lung Transplantation: A Multicenter Study

The Journal of Heart and Lung Transplantation

2005

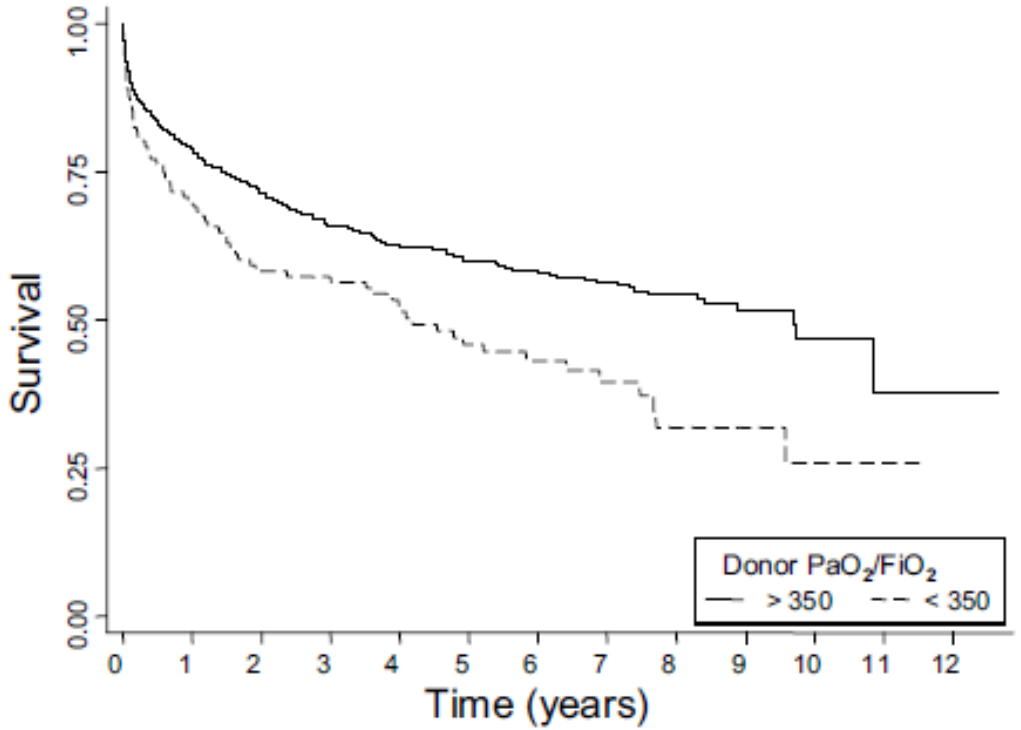


Figure 1. Graft survival according to donor Pao_2/Fio_2 before harvest: <350 (n = 111) and >350 (n = 584). Survival is adjusted for recipient age, underlying disease, and graft ischemic time.

NEI CASI CONTROVERSI

A B C D

- ✓ ***Preservation***
- ✓ ***Assessment***
- ✓ ***Reconditioning***
- ✓ ***(Immunomodulation)***

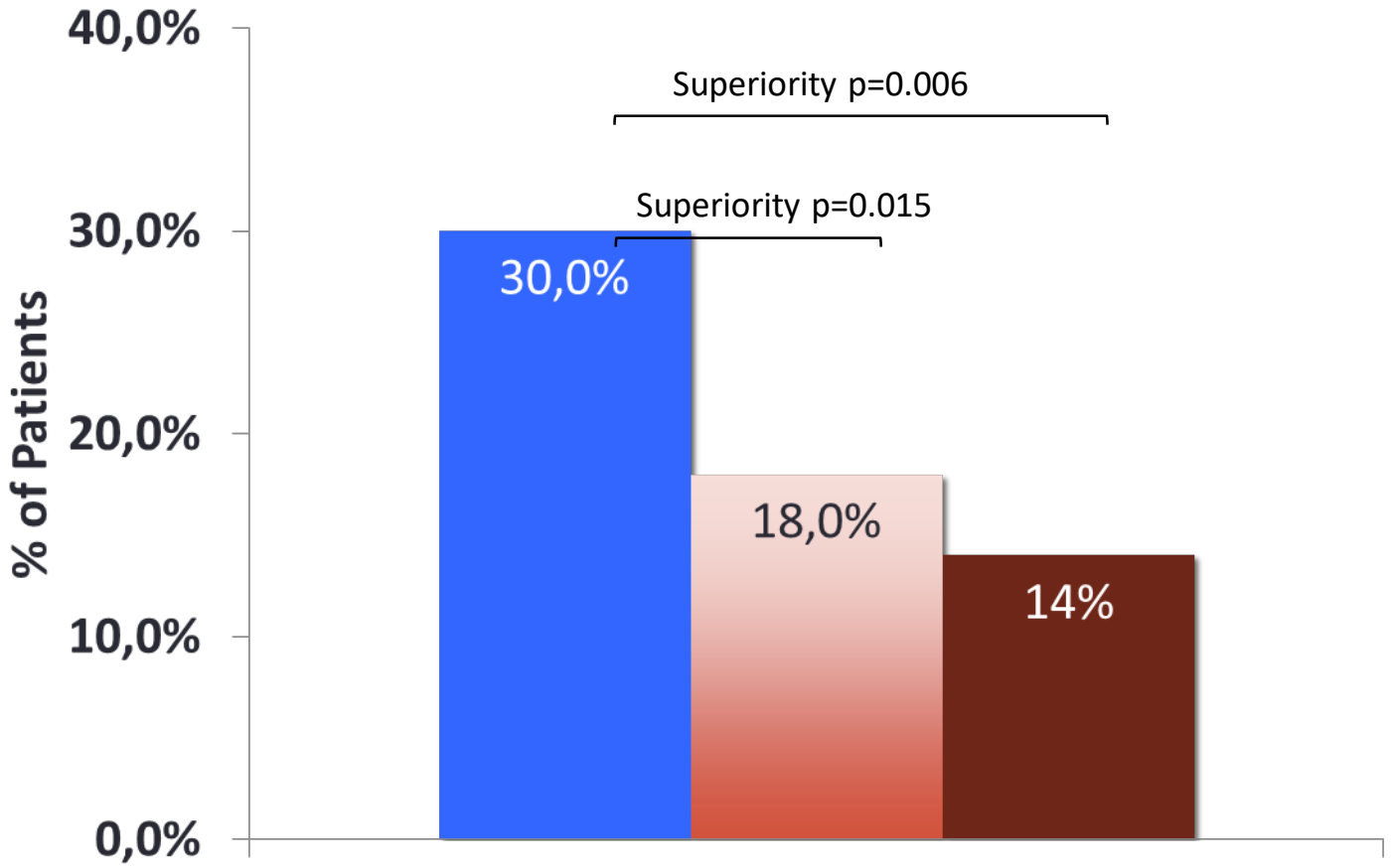
Lancet Respir Med 2018;
6: 357-67

Normothermic ex-vivo preservation with the portable Organ Care System Lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study

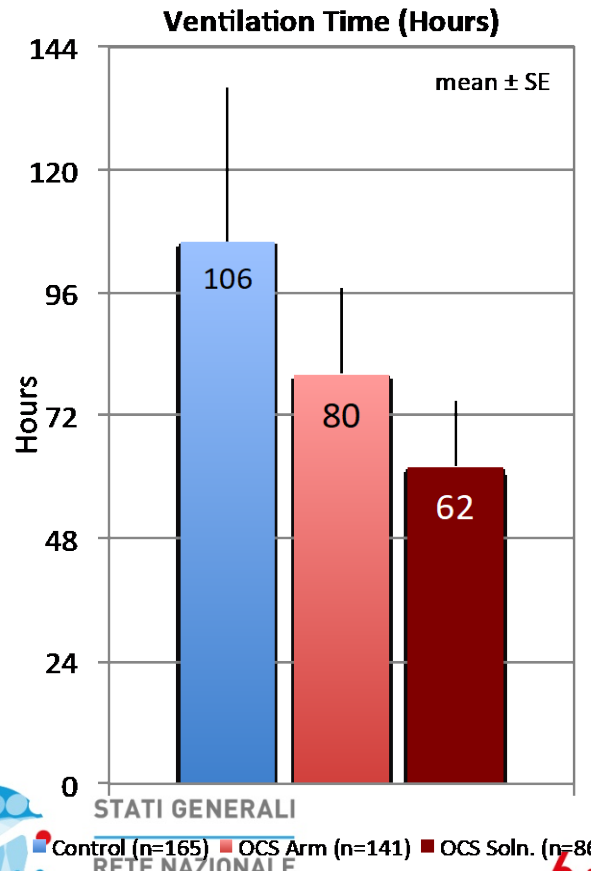
Gregor Warnecke, Dirk Van Raemdonck, Michael A Smith, Gilbert Massard, Jasleen Kukreja, Federico Rea, Gabriel Loor, Fabio De Robertis, Jayan Nagendran, Kumud K Dhital, Francisco Javier Moradiellos Díez, Christoph Knosalla, Christian A Bermudez, Steven Tsui, Kenneth McCurry, I-Wen Wang, Tobias Deuse, Guy Lesèche, Pascal Thomas, Igor Tudorache, Christian Kühn, Murat Avsar, Bettina Wiegmann, Wiebke Sommer, Arne Neyrinck, Marco Schiavon, Fiorella Calabrese, Nichola Santelmo, Anne Olland, Pierre-Emanuel Falcoz, Andre R Simon, Andres Varela, Joren C Madsen, Marshall Hertz, Axel Haverich, Abbas Ardehali

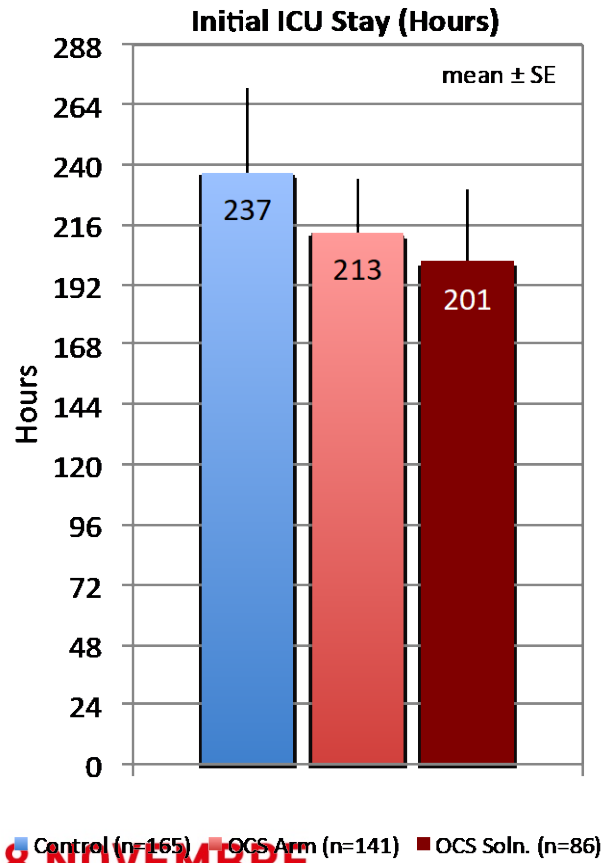
Interpretation The INSPIRE trial met its primary effectiveness and safety endpoints. Although no short-term survival benefit was reported, further research is needed to see whether the reduced incidence of PGD3 within 72 h of a transplant might translate into earlier recovery and improved long-term outcomes after lung transplantation.

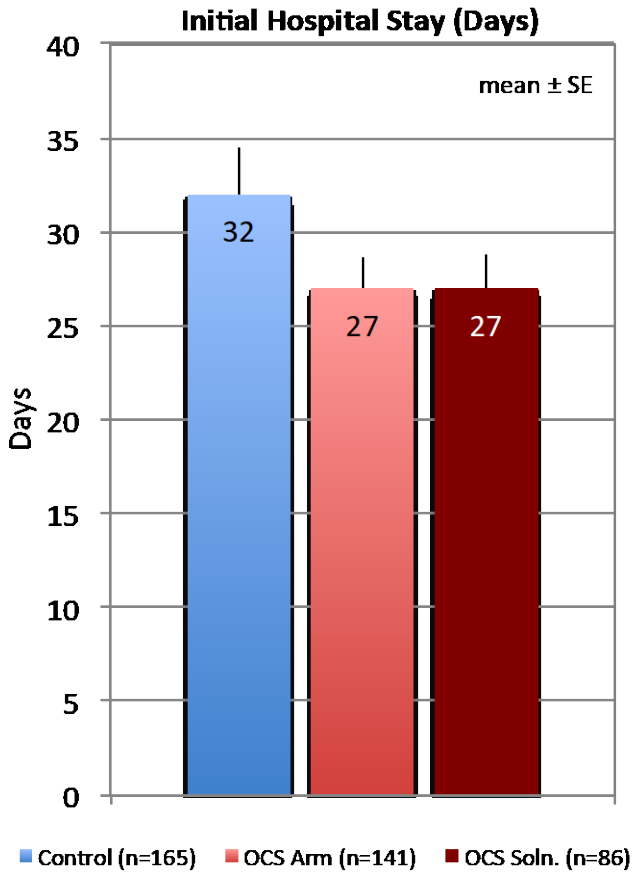
INCIDENCE OF PGD 3 WITHIN 72 HOURS (T0 - T72 HOURS)



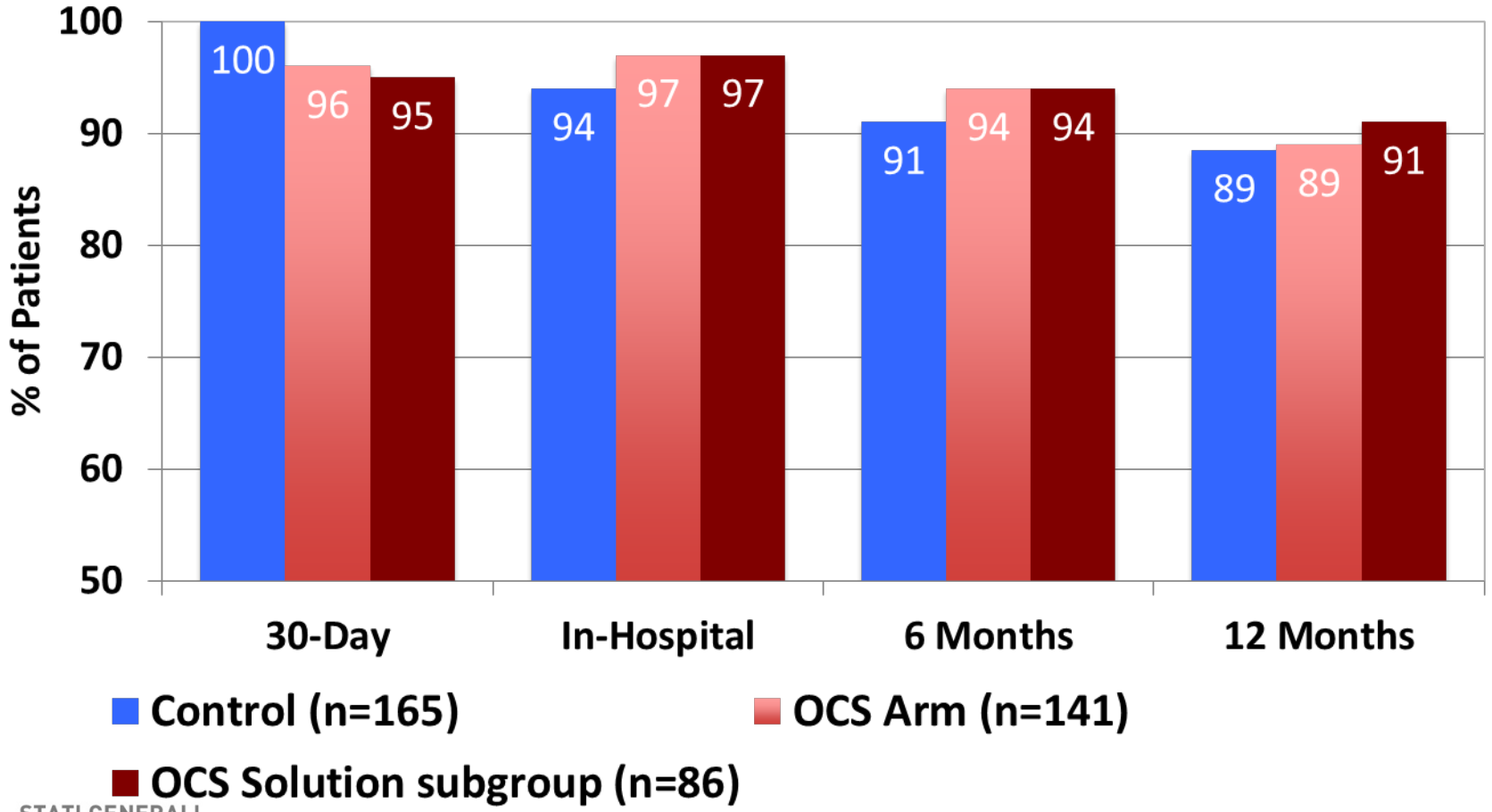
Trend of Better Vent and ICU Time and Total LOS







OCS LUNG INSPIRE SURVIVAL



Lancet Respir Med 2019;
7: 975–84

Portable normothermic ex-vivo lung perfusion, ventilation, and functional assessment with the Organ Care System on donor lung use for transplantation from extended-criteria donors (EXPAND): a single-arm, pivotal trial

Gabriel Loor, Gregor Warnecke, Mauricio A Villavicencio, Michael A Smith, Jasleen Kukreja, Abbas Ardehali, Matthew Hartwig, Mani A Daneshmand, Marshall I Hertz, Stephen Huddleston, Axel Haverich, Joren C Madsen, Dirk Van Raemdonck

Findings Between Jan 23, 2014, and Oct 23, 2016, 93 lung pairs were perfused, ventilated, and assessed on the OCS Lung. 12 lungs did not meet OCS transplantation criteria so 81 lungs were suitable for transplantation. Two lungs were excluded for logistical reasons, hence 79 (87%) of eligible lungs were transplanted. The primary endpoint was achieved in 43 (54%) of 79 patients and did not meet the objective performance goal. 35 (44%) of 79 patients had PGD3 within the initial 72 h. 78 (99%) of 79 patients had survived at 30 days post-transplant. The mean number of lung graft-related serious adverse events (respiratory failure and major pulmonary-related infection) was 0·3 events per patient (SD 0·5).

Interpretation Despite missing the objective primary endpoint, the portable OCS Lung resulted in 87% donor lung use for transplantation with excellent clinical outcomes. Many lungs declined by other transplant centres were successfully transplanted using this new technology, which implies its use has the potential to increase the number of lung transplants performed worldwide. Whether similar outcomes could be obtained if these lungs were preserved on ice is unknown and remains an area for future research.

	Participants (n=79)
Donors	
One inclusion criterion	
Age ≥55 years	22 (28%)
DCD	16 (20%)
Expected cross-clamp time >6 h	11 (14%)
PaO_2:FiO_2 ≤300 mm Hg	9 (11%)
Two inclusion criteria	
DCD and expected cross-clamp time >6 h	6 (8%)
PaO_2:FiO_2 ≤300 mm Hg and expected cross-clamp time >6 h	5 (6%)
PaO_2:FiO_2 ≤300 mm Hg and age ≥55 years	3 (4%)
DCD and age ≥55 years	3 (4%)
DCD and PaO_2:FiO_2 ≤300 mm Hg	1 (1%)
Expected cross-clamp time >6 h and age ≥55 years	1 (1%)
Three inclusion criteria	
PaO_2:FiO_2 ≤300 mm Hg, expected cross-clamp time >6 h, and age ≥55 years	2 (3%)
Total number of donors according to inclusion criteria	
DCD	26 (33%)
Donor age ≥55 years	31 (39%)
Expected cross-clamp time >6 h	25 (32%)
PaO_2:FiO_2 ≤300 mm Hg	20 (25%)
Donors with multiple criteria	21 (27%)

DONOR OR RECIPIENT ?

Marginal donor lungs: A reassessment

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Conclusions: **Nonguideline recipients appear to have acceptable early mortality, except when they received extended donor lungs.**

	30-Day mortality
Standard donor + guideline recipient	6.5% (3/46)
Standard donor + nonguideline recipient	5.3% (1/19)
Extended donor + guideline recipient	15.6% (7/45)
Extended donor + nonguideline recipient	22.2% (4/18)

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Recipient outcome: Subgroups 30-day mortality

CONCLUSIONI

- L’utilizzo di donatori con criteri estesi è pratica clinica ormai utIlizzata correntemente
- Esistono alcuni criteri tuttavia che devono essere considerati prima di essere violati (PaO2, secrezioni)
- Nei casi dubbi l’utilizzo di device ex-vivo può aiutare a valutare l’organo più correttamente (necessario nel DCD)
- Importante sempre il match con il paziente ricevente