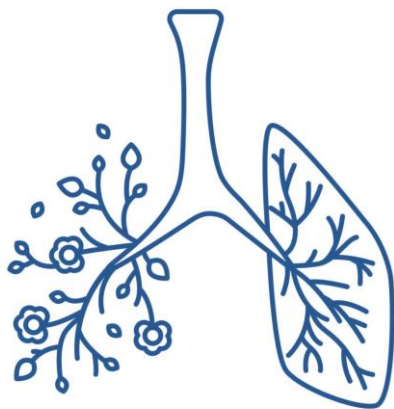


Lung Transplantation for Patients with ILD



서울대학교병원 호흡기내과
최선미

- **Introduction**
- **Indication of lung transplantation**
- **Lung allocation system**
- **Outcome of lung transplantation**
- **Special consideration in ILD patients**
- **Conclusion**

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Father of heart and lung transplantation



Vladimir Demikhov

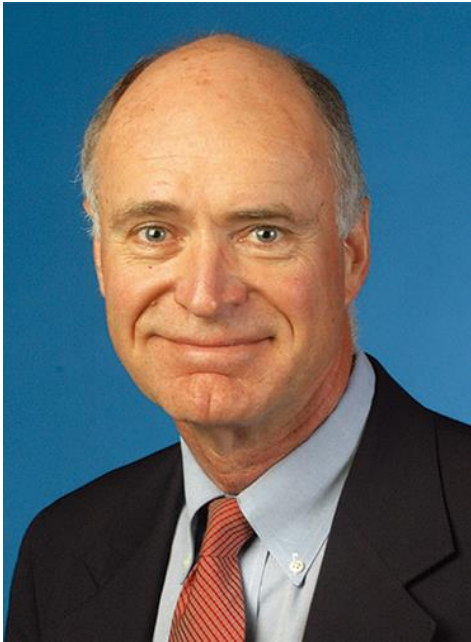
- 1937 – first cardiac assist device
- 1946 – first intrathoracic heterotopic heart transplant
- 1946 – first heart-lung transplant
- 1947 – first lung transplant
- 1948 – first liver transplant
- 1951 – first orthotopic (correctly positioned) heart transplant
- 1952 – first mammary– coronary anastomosis
- 1953 – first successful experimental coronary artery bypass operation
- 1954 – first head transplant

First lung transplantation in 1963



- James Hardy (University of Mississippi Medical Center)
- Patient – 58/M with Lung cancer obstructing main bronchus and obstructive pneumonia
- The recipient died on day 18 d/t renal failure and infection

First Heart-lung transplant in 1981



“The appearance of Mary Gohlke’s totally empty chest was indeed a dramatic moment,” Reitz remembered. “I wondered, ‘Is this really going to work out?’

- Bruce Reitz and colleagues (Stanford)
- First successful transplantation of the heart and one lung
- 45-year-old woman diagnosed with primary pulmonary hypertension

First long term successful LT in 1983



- Joel Cooper (Toronto group)
- Right lung transplant
- Recipient: Tom Hall, 58-year old man with pulmonary fibrosis, “It is my privilege to be the 44th patient”
- Survived for nearly 5 years

Double lung transplant in 1986



- Alexander Patterson and Joel Cooper
- First successful double LT with tracheal anastomosis
- 42-year-old Toronto woman with emphysema secondary to alpha₁-antitrypsin deficiency

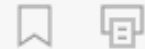
[의학] 국내 최초의 폐 이식수술, 결과도 "성공"

"살아있는게 꿈같소"...이식받은 황씨 빠른 회복 #.

1996년 세브란스병원

조선일보

입력 1996.07.19 15:31



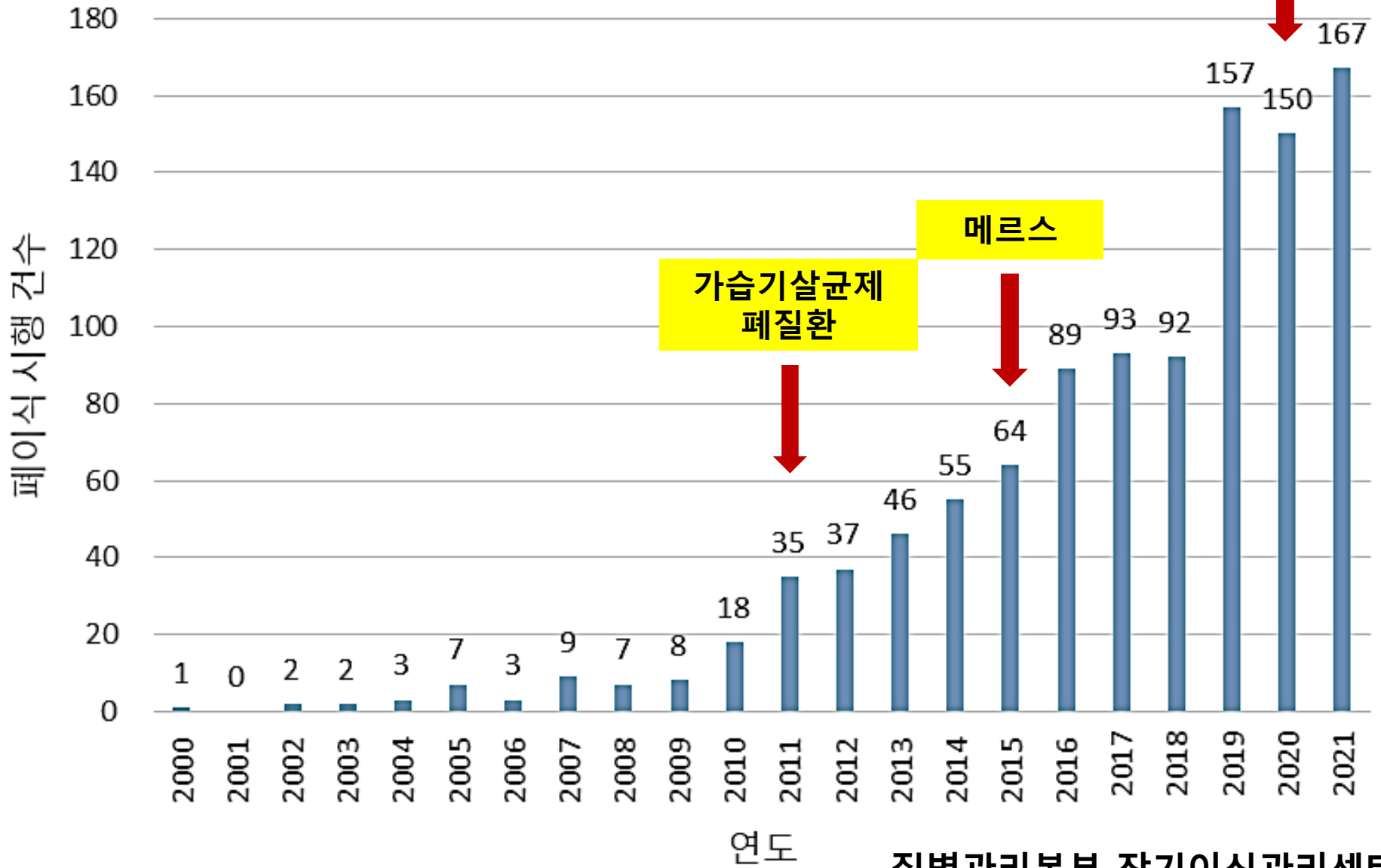
"살아있는게 꿈같소"...이식받은 황씨 빠른 회복 #.

『수술이 잘 됐다니 기쁘긴 하지만 온 몸이 쭈시고 아파 죽겠습니다.』 .

지난 7월12일 낮 12시30분, 서울 신촌세브란스병원 심장혈관센터 중환자 집중처치실. 집중처치실 내에 있는 무균 격리병실에서 황모씨(53)가 미음을 먹고 있었다.

황씨는 지난 7월7일 국내 최초로 뇌사자 이모군(17)의 폐를 이식받은 폐섬유증 환자. 수술 전 3개월여동안 중환자실에서 생사의 기로에 서 있다 국내 최초로 폐이식을 받은 장본인이다. 상상했던 것보다 훨씬 상태가 좋아보이는 그에게 무균 병실 밖에서 전화로 『기분이 어떨냐』 고 물었다.

국내 폐이식 현황



Lung transplantation for severe COVID-19-related ARDS

Ryoung-Eun Ko, Dong Kyu Oh, Sun Mi Choi , Sunghoon Park, Ji Eun Park, Jin Gu Lee, Young Tae Kim and Kyeongman Jeon ; on behalf of the Korean Lung Transplantation Study Group

Abstract

Background: Lung transplantation (LT) is the gold standard for various end-stage chronic lung diseases and could be a salvage therapeutic option in acute respiratory distress syndrome (ARDS). However, LT is uncertain in patients with coronavirus disease 2019 (COVID-19)-related ARDS who failed to recover despite optimal management including extracorporeal membrane oxygenation (ECMO). This study aims to describe the pooled experience of LT for patients with severe COVID-19-related ARDS in Korea.

Methods: A nationwide multicenter retrospective observational study was performed with consecutive LT for severe COVID-19-related ARDS in South Korea (June 2020–June 2021). Data were collected and compared with other LTs after bridging with ECMO from the Korean Organ Transplantation Registry.

Results: Eleven patients with COVID-19-related ARDS underwent LT. The median age was 60.0 years [interquartile range (IQR), 57.5–62.5; six males]. All patients were supported with venovenous ECMO at LT listing and received rehabilitation before LT. Patients were transplanted at a median of 49 (IQR, 32–66) days after ECMO cannulation. Primary graft dysfunction within 72 h of LT developed in two (18.2%). One patient expired 4 days after LT due to sepsis and one patient underwent retransplantation for graft failure. After a median follow-up of 322 (IQR, 299–397) days, 10 patients are alive and recovering well. Compared with other LTs after bridging with ECMO ($n=27$), post-transplant outcomes were similar between the two groups.

Conclusions: LT in patients with unresolving COVID-19-related ARDS were effective with reasonable short-term outcome.

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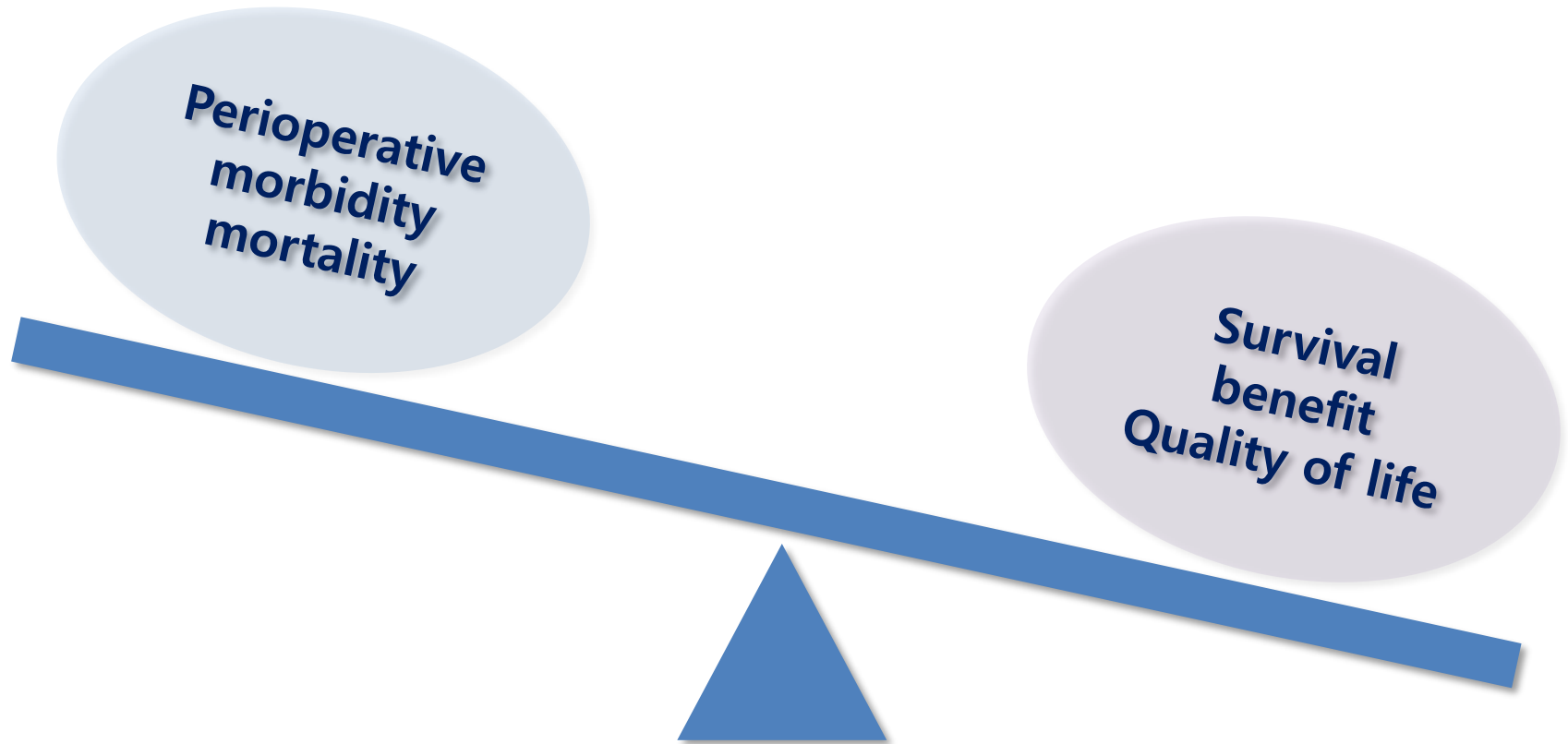
Sun Mi Choi
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Seoul National University
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South Korea

- Introduction
- **Indication of lung transplantation**
- Lung allocation system
- Outcome of lung transplantation
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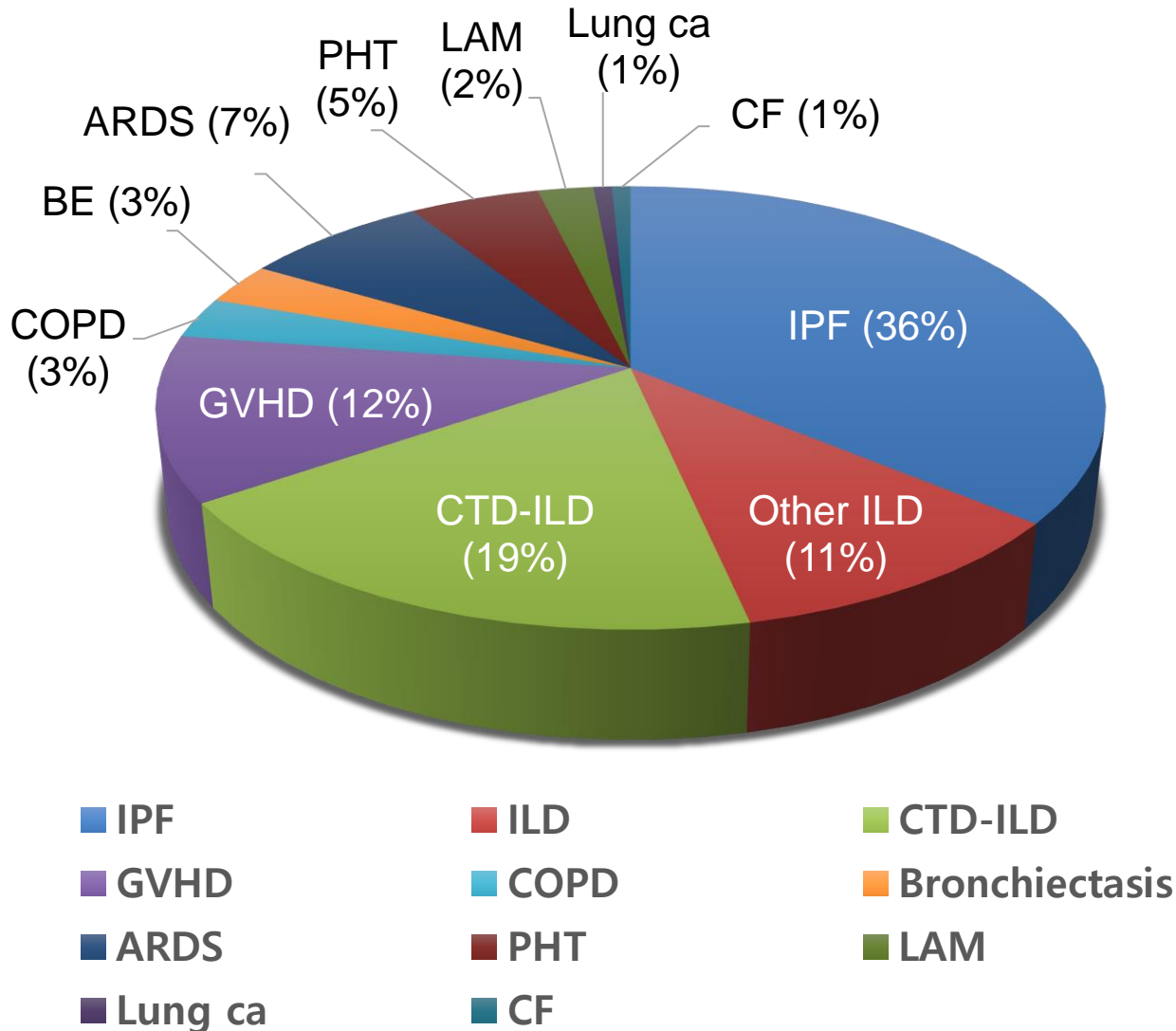
International Guidelines for the selection of lung TPL: 2021 update

- Lung TPL
 - Should be considered for adults **with chronic, end-stage lung disease who meet all the following general criteria:**
 - ✓ High (>50%) risk of death from lung disease within 2 years if lung TPL is not performed.
 - ✓ High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function.
- Primary goal of lung TPL: to improve **survival and quality of life** → Not cure!

Benefit vs. Risk of transplantation



Indication of lung transplantation in SNUH



Diagnosis	N	(%)
IPF	48	36.1
CTD-ILD	25	18.8
Other ILD	14	10.5
GVHD	16	12.0
COPD	4	3.0
Bronchiectasis	4	3.0
ARDS	10	7.5
Pulmonary hypertension	7	5.3
LAM	3	2.3
Lung cancer	1	0.8
CF	1	0.8

Slide courtesy of prof HJ. Lee

Absolute contraindications

- 1. Lack of patient willingness or acceptance of transplant
- 2. Malignancy with high risk of recurrence or death related to cancer
- 3. GFR < 40 mL/min/1.73m² unless being considered for multi-organ transplant
- 4. ACS or MI within 30 days (excluding demand ischemia)
- 5. Stroke within 30 days
- 6. LC with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant
- 7. Acute liver failure
- 8. ARF with rising creatinine or on dialysis and low likelihood of recovery

Absolute contraindications

- 9. Septic shock
- 10. Active extrapulmonary or disseminated infection
- 11. Active tuberculosis infection
- 12. HIV infection with detectable viral load
- 13. Limited functional status (e.g. non-ambulatory) with poor potential for post-transplant rehabilitation
- 14. Progressive cognitive impairment
- 15. Repeated episodes of non-adherence without evidence of improvement
- 16. Active substance use or dependence including current tobacco use, vaping, marijuana smoking, or IV drug use
- 17. Other severe uncontrolled medical condition expected to limit survival after transplant

Risk factors with high or substantially increased risk

- 1. Age > 70 years
- 2. Severe coronary artery disease that requires CABG at transplant
- 3. Reduced left ventricular ejection fraction < 40%
- 4. Significant cerebrovascular disease
- 5. Severe esophageal dysmotility
- 6. Untreatable hematologic disorders
- 7. BMI > 35 kg/m²
- 8. BMI < 16 kg/m²
- 9. Limited functional status with potential for post-transplant rehabilitation
- 10. Psychiatric, psychological or cognitive conditions with potential to interfere with medical adherence without sufficient support systems

Risk factors with high or substantially increased risk

- 11. Unreliable support system or caregiving plan
- 12. Lack of understanding of disease and / or transplant
- 13. [Mycobacterium abscessus infection](#)
- 14. Lomentospora prolificans infection
- 15. Burkholderia cenocepacia or gladioli infection
- 16. Hepatitis B or C infection with detectable viral load and liver fibrosis
- 17. Chest wall or spinal deformity expected to cause restriction after transplant
- 18. [Extracorporeal life support](#)
- 19. Retransplant <1 year following initial lung transplant
- 20. [Retransplant for restrictive CLAD](#)
- 21. Retransplant for AMR as etiology for CLAD

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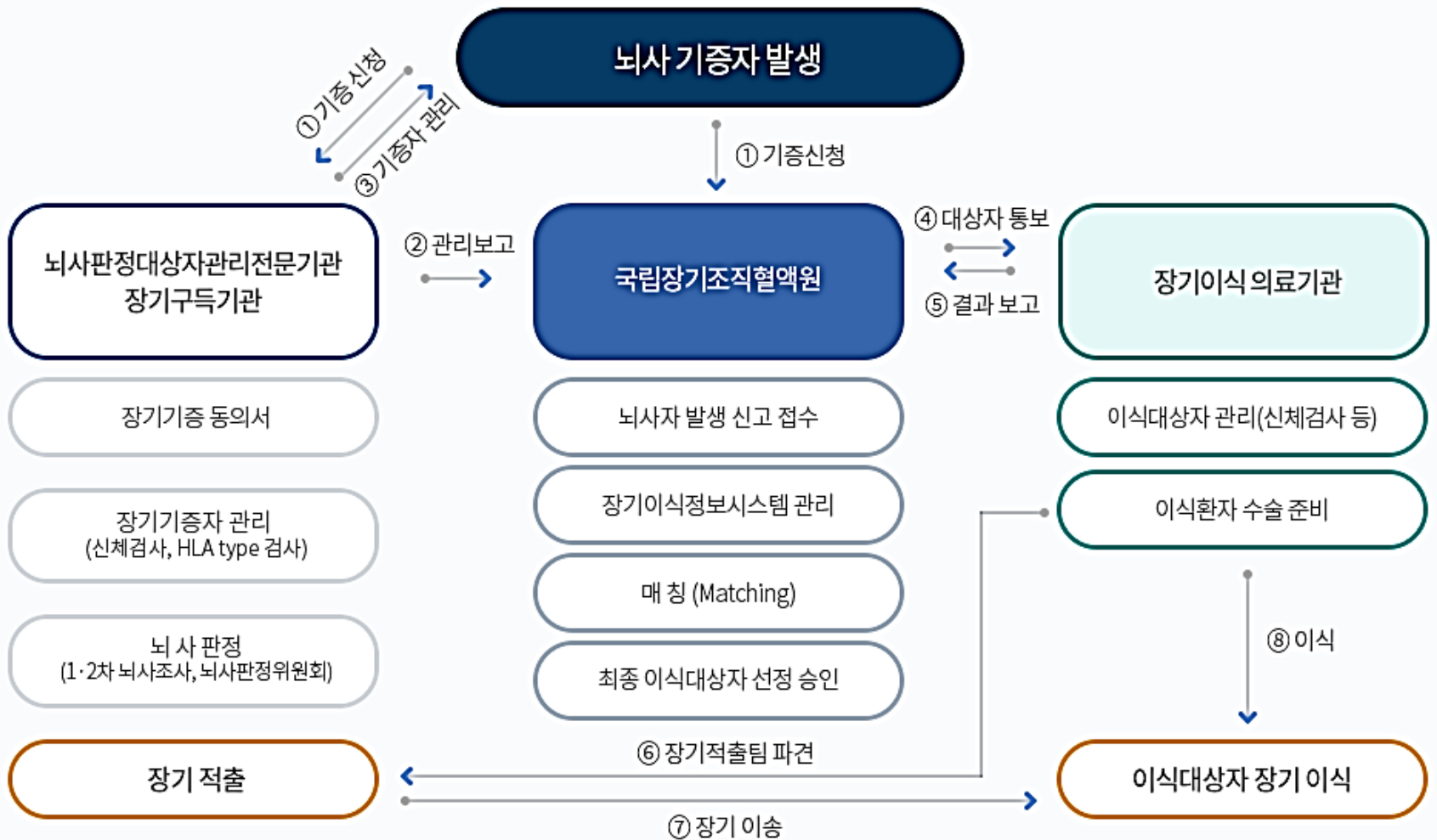
Lung allocation

- Among the 3500 transplants worldwide annually
- Waiting time based (Japan)
- Urgency based (Korea)
- Score based (both urgency and benefit are considered)
 - used in worldwide
- 60 % are allocated by lung allocation score (LAS)
(US 2005;updated 2020, Germany 2011, Netherlands)

국내 이식 시스템

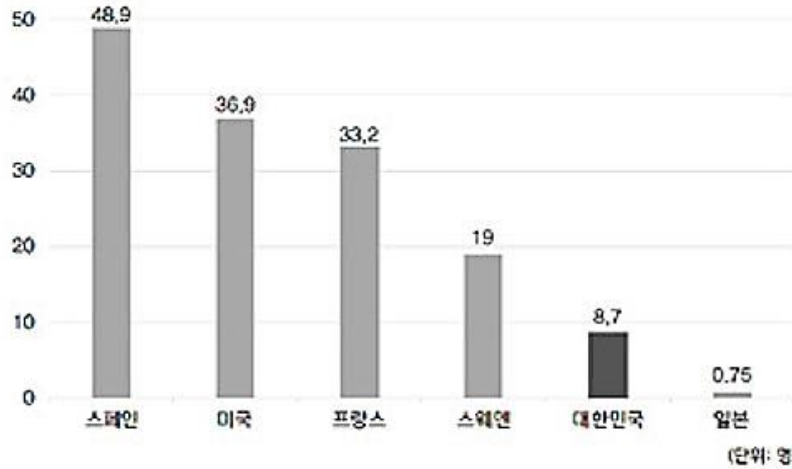
- 2000년 2월 장기기증 및 이식에 관한 법률 시행 및 장기이식관리센터(Korean Network for Organ Sharing, KONOS) 설립 (현 보건복지부 하 국립장기조직혈액관리원)
- 뇌사판정대상자관리전문기관 (HOPO)

뇌사 장기기증 및 이식



국내 뇌사기증자

국가별 인구 100만 명당 장기 기증자수

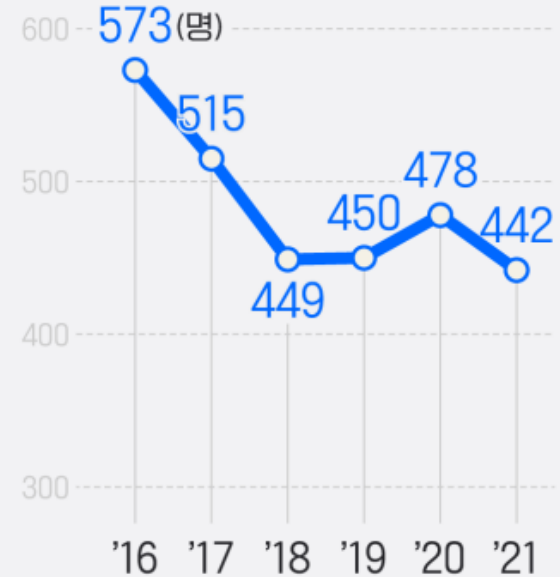


장기 기증 현황

*2021년 기준

이식 장기	1,478건
기증자	442명
뇌사 기증자 1인당 평균 이식 장기	3.34

국내 뇌사 장기 기증 추이



국가별 뇌사/생존시 기증자

표 1-1-1. 뇌사 기증자 - 국가별

(단위: 명, PMP)

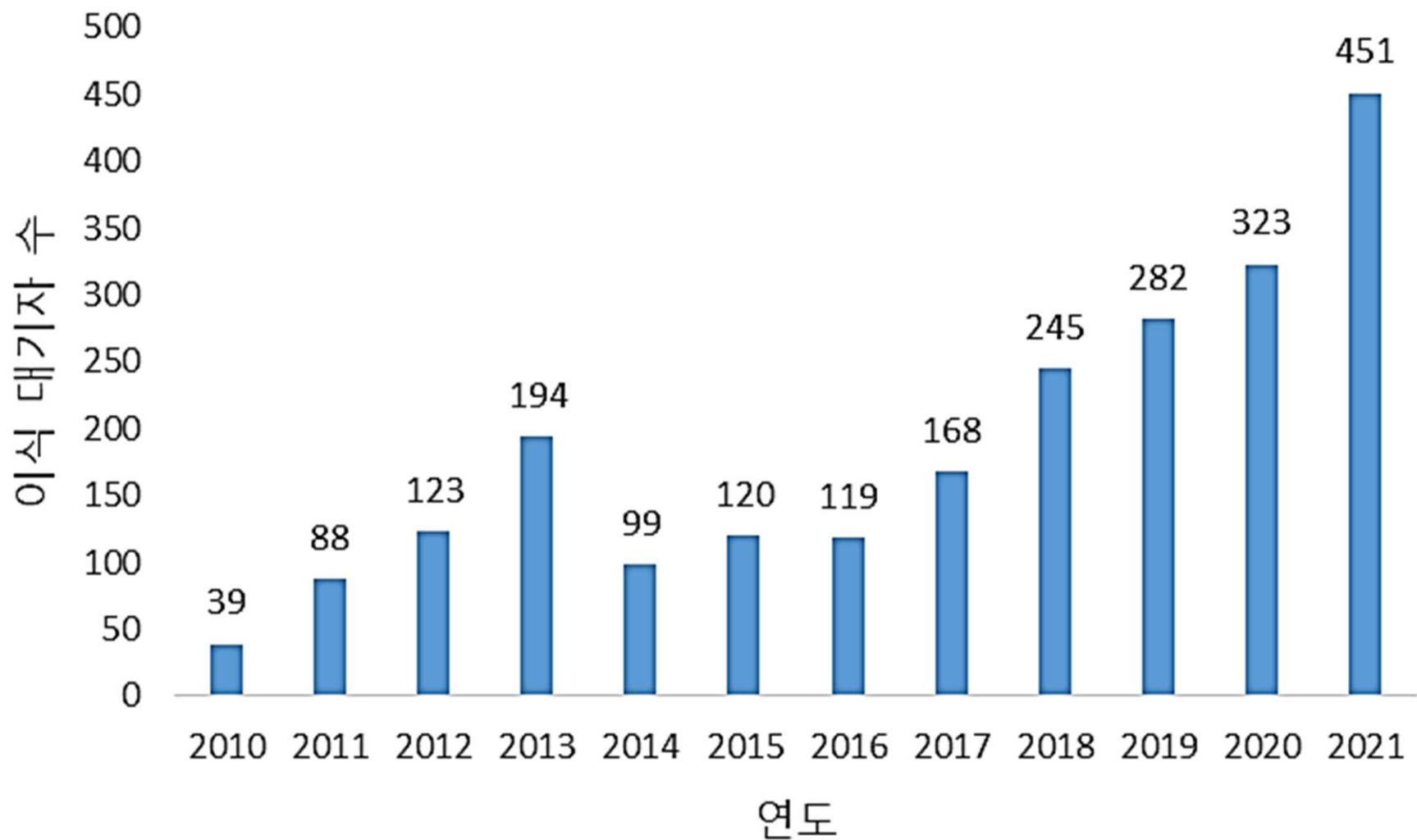
구분	스페인	미국	이탈리아	영국	독일	대한민국	
2017	뇌사기증자 (명)	2,182	10,284	1,714	1,492	797	515
	뇌사기증율 (PMP)	46.9	31.96	28.2	23.05	9.7	9.95
2018	뇌사기증자 (명)	2,241	10,721	1,681	1,619	955	449
	뇌사기증율 (PMP)	48.0	33.32	27.73	24.52	11.5	8.66
2019	뇌사기증자 (명)	2,301	11,870	1,495	1,653	932	450
	뇌사기증율 (PMP)	48.9	36.88	24.7	24.88	11.2	8.68
2020	뇌사기증자 (명)	1,777	12,588	1,303	1,248	913	478
	뇌사기증율 (PMP)	37.4	38.03	21.6	18.68	11.0	9.22
2021	뇌사기증자 (명)	1,905	13,863	1,458	1,350	933	442
	뇌사기증율 (PMP)	40.8	41.6	24.1	19.8	11.1	8.56

표 1-2-1. 생존시 기증자 - 국가별

(단위: 명, PMP)

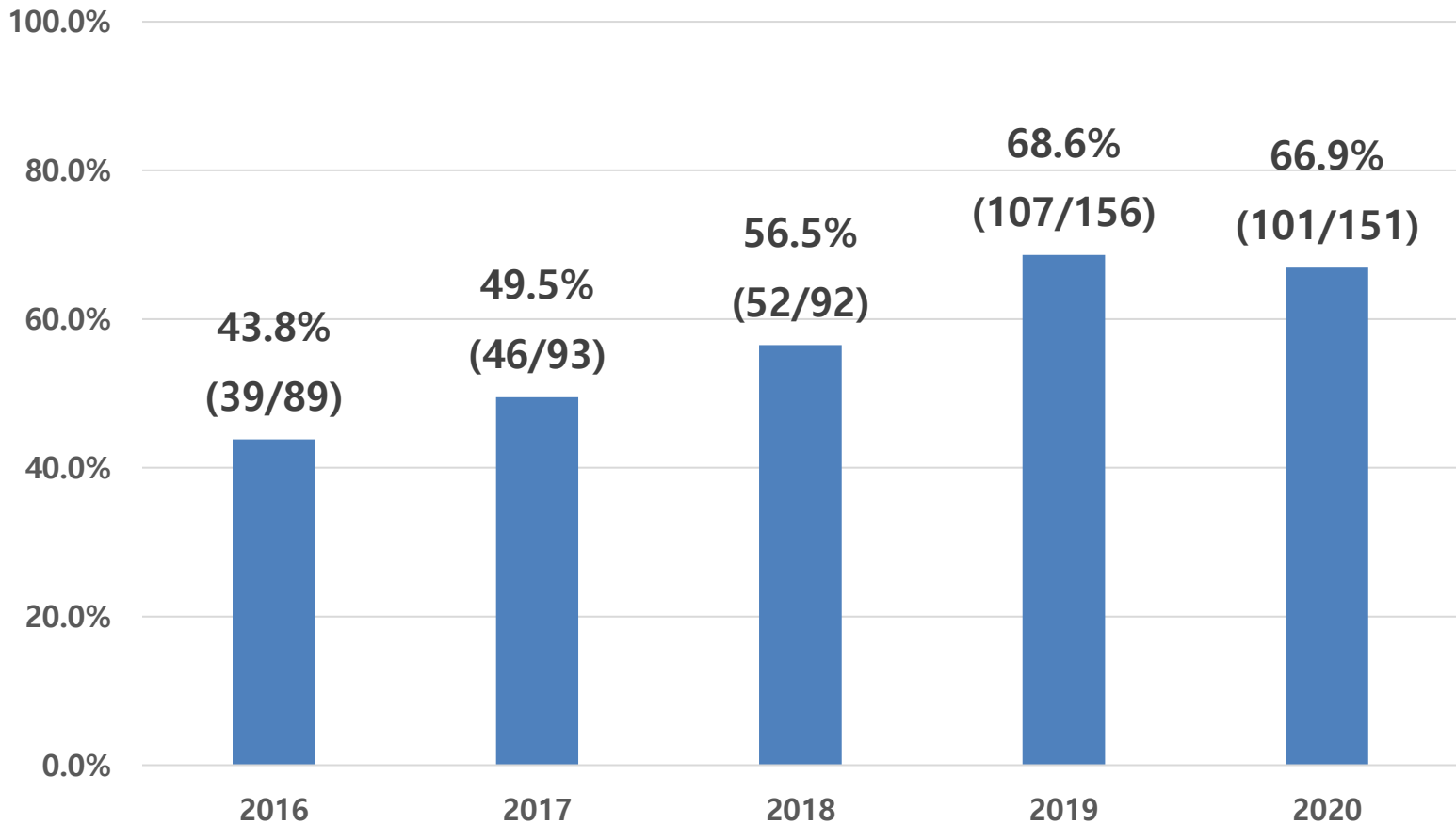
구분	스페인	미국	이탈리아	영국	독일	대한민국	
2017	생존시기증자 (명)	353	6,183	325	1,010	618	2,293
	생존시기증율 (PMP)	7.57	19.21	5.4	15.60	7.5	44.28
2018	생존시기증자 (명)	289	6,833	312	1,054	695	2,405
	생존시기증율 (PMP)	6.19	21.24	5.15	15.96	8.4	46.4
2019	생존시기증자 (명)	335	7,399	364	1,041	575	2,685
	생존시기증율 (PMP)	7.17	22.99	6	15.67	6.9	51.78
2020	생존시기증자 (명)	268	5,726	303	602	502	2,578
	생존시기증율 (PMP)	5.77	17.29	5.01	9.01	6	49.74
2021	생존시기증자 (명)	324	6,538	378	754	529	2,638
	생존시기증율 (PMP)	6.92	19.6	7.2	11.0	6.36	51.09

국내 폐이식 대기자 현황



응급도 0에서 폐이식 받은 국내 환자의 비율

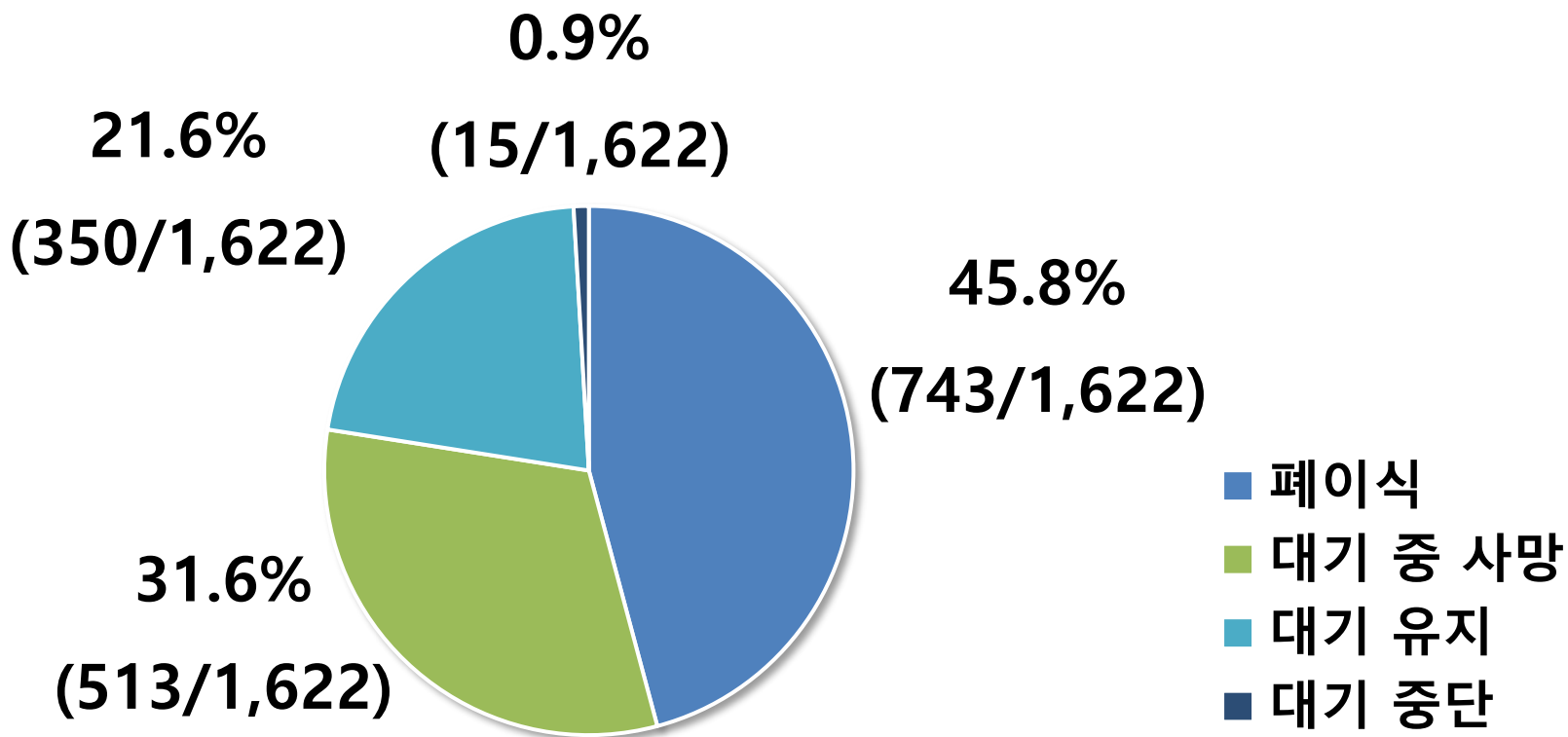
2016년: 43.8% → 2020년: 66.9%



응급도 0에서 폐이식 받은 환자 비율 비교

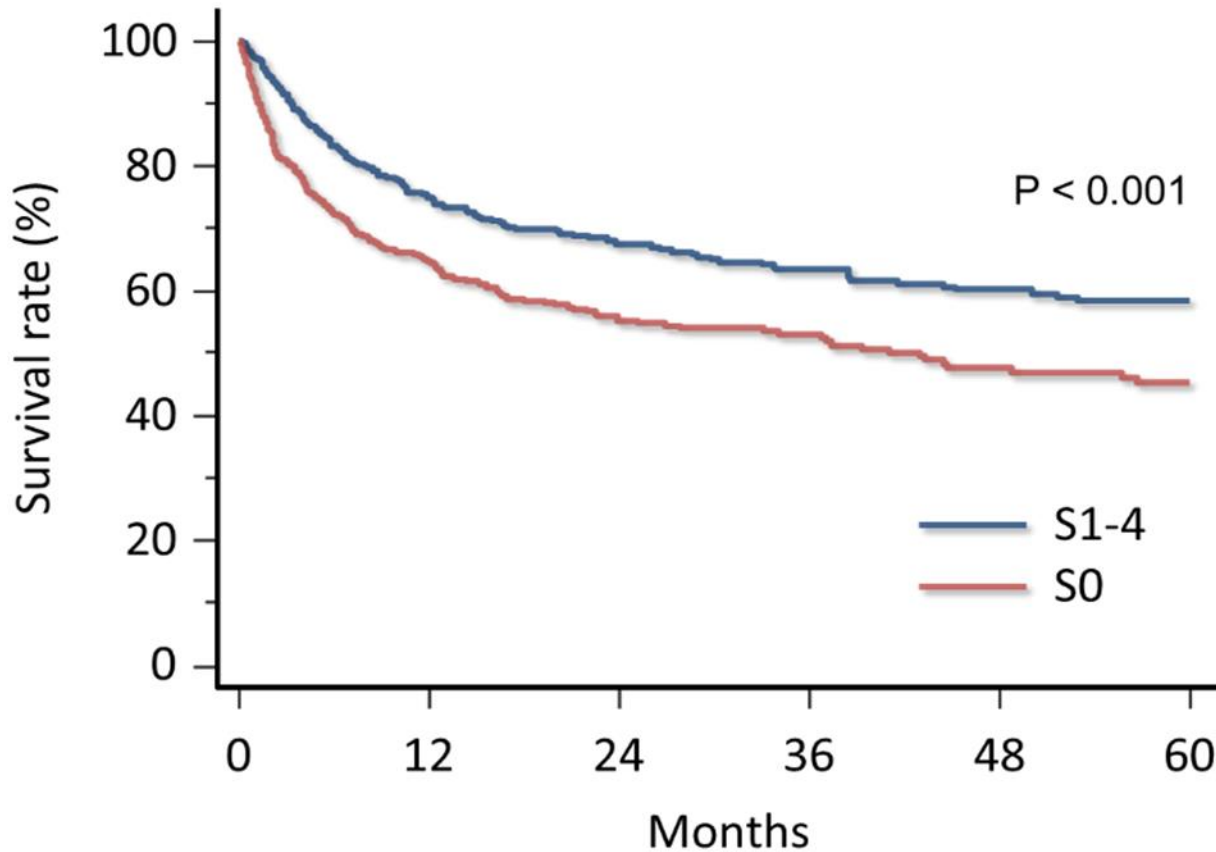
	한국 (n=156)	미국 (n=2,707)
기계환기기 또는 ECMO 적용 (응급도 0)	107 (68.6%)	259 (9.6%)
기계환기기와 ECMO 모두 적용하지 않음 (응급도 1-4)	49 (31.4%)	2,448 (90.4%)

폐이식 대기 등록 1년 후 예후

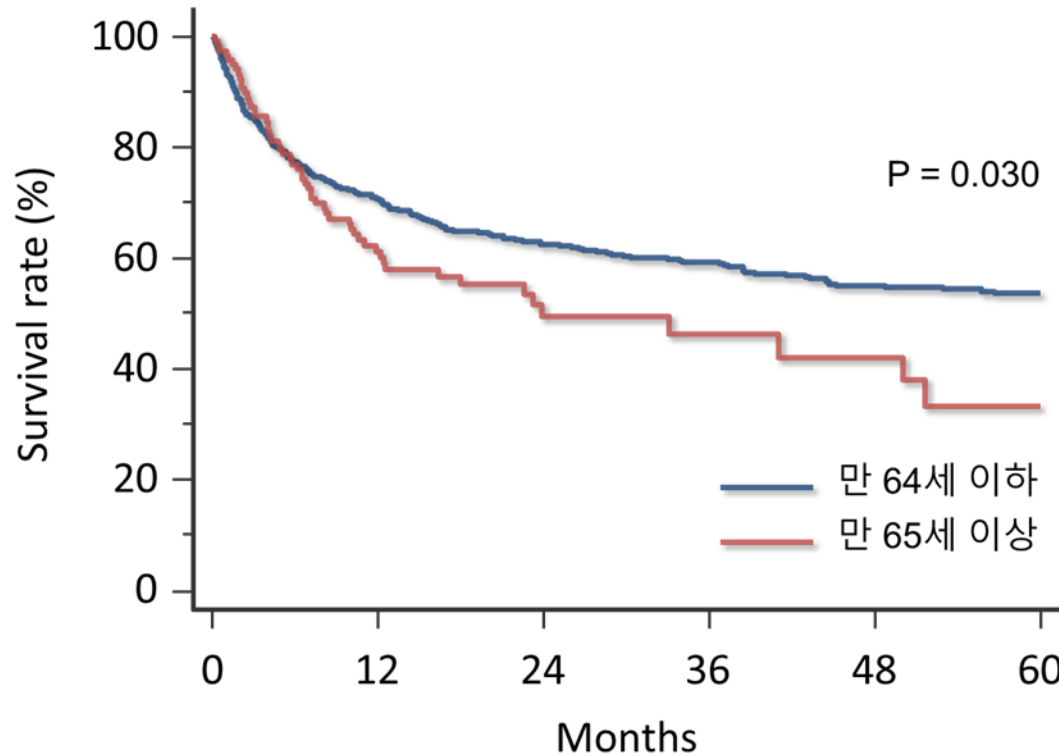


(2009.09.-2020.12.)

응급도에 따른 폐이식 후 5년 생존율



연령에 따른 이식 후 생존율의 차이



	만 64세 이하 (n=719)	만 65세 이상 (n=117)	P-value
1년 생존율	70.5%	61.1%	0.110
3년 생존율	59.1%	46.2%	0.060
5년 생존율	53.6%	33.0%	0.030

국내 폐 응급도 기준 변경 (2023. 5. 1)

구분	현행	개선(안)
응급도0	<p>입원한 환자로 다음 한 가지 이상 해당하여야 한다.(8일 이내 재등록)</p> <p>① 호흡부전증으로 인공호흡기를 부착중인 환자 ② 체외막형 심폐기를 가동 중인 환자</p>	<p>입원한 환자로 다음 한 가지 이상 해당 하여야 한다.(8일 이내 재등록, 19세 미만 이식대기자는 재등록 횟수 제한이 없으며, 19세 이상은 8일마다 3회까지 등록 가능)</p> <p>① 호흡부전증으로 인공호흡기를 부착중인 환자 ② 체외막형 심폐기를 가동 중인 환자</p>
응급도1	<p>다음 한 가지 이상 해당하여야 한다. (60일마다 재등록하며 검사결과는 검사시점과 상관없이 인정한다)</p> <p>① 산소투여없이 측정동맥혈가스검사상 PaO₂ < 55mmHg ② 평균 폐 동맥혈압 > 65mmHg, 또는 평균 우심방 혈압 > 15mmHg ③ Cardiac index < 2L/min/m² 인 경우 ④ 동맥혈검사 상 PCO₂ ≥ 80mmHg인 경우 ⑤ 입원환자 중 고유량 비강 캐놀라(highflow nasal cannula) 30L FiO₂ ≥ 0.6으로 2주 이상 유지중인 경우(유지 중에만 인정) ⑥ <u>(신 설)</u></p>	<p>다음 한 가지 이상 해당하여야 한다. (60일마다 재등록하며 검사결과는 검사시점과 상관없이 인정한다)</p> <p>① 산소투여없이 측정동맥혈가스검사상 PaO₂ < 55mmHg ② 평균 폐 동맥혈압 > 65mmHg, 또는 평균 우심방 혈압 > 15mmHg ③ Cardiac index < 2L/min/m² 인 경우 ④ 동맥혈검사 상 PCO₂ ≥ 80mmHg인 경우 ⑤ 입원환자 중 고유량 비강 캐놀라(highflow nasal cannula) 30L FiO₂ ≥ 0.6으로 2주 이상 유지중인 경우(유지 중에만 인정) ⑥ 인공호흡기나 체외막형 심폐기를 적용 중인 이식대기자 중 응급도 '0'에 해당되지 않는 경우</p>

수혜자 선정 기준

- 1) 응급도가 가장 높은 이식대기자
- 2) 다음의 순서
 - 가) 기증자와 같은 권역, 기증자와 같은 혈액형
 - 나) 기증자와 다른 권역, 기증자와 같은 혈액형
 - 다) 기증자와 같은 권역, 기증자로부터 수혈이 가능한 혈액형
 - 라) 기증자와 다른 권역, 기증자로부터 수혈이 가능한 혈액형
- 4) 다음의 항목별 점수의 합계가 가장 높은 사람 선정
 - 가) 대기 기간
 - 나) 기증전력자 등 인지 여부
 - 다) 나이

가산점 항목

항목	내용	점수
(1) 대기 기간*	응급도 0 (최대 8점)	0.5점/일 가산
	응급도 1 이상 (최대 8점)	(심장)0.5점/주 가산
		(폐)0.25점/주 가산 응급도 '0' 이었다가 응급도 '1'로 등록된 경우 응급도 '0'에서의 대기기간을 가산함
(2) 기종 전력자 등인지 여부	과거에 장기등을 기종한 경우 (본인 생존 기종)	2점
	배우자, 직계 존·비속 중에서 뇌사 기종을 한 경우	
	형제자매 중에서 뇌사 기종을 한 경우	1점
	4촌 이내 친족 중에서 뇌사 기종을 한 경우	1점
(3) 나이	19세 미만	2점
	(심장) 19세 이상~70세 미만	1점
	(폐) 19세 이상~65세 미만	

뇌사추정자 전자통보 장기조직기증원(KODA)

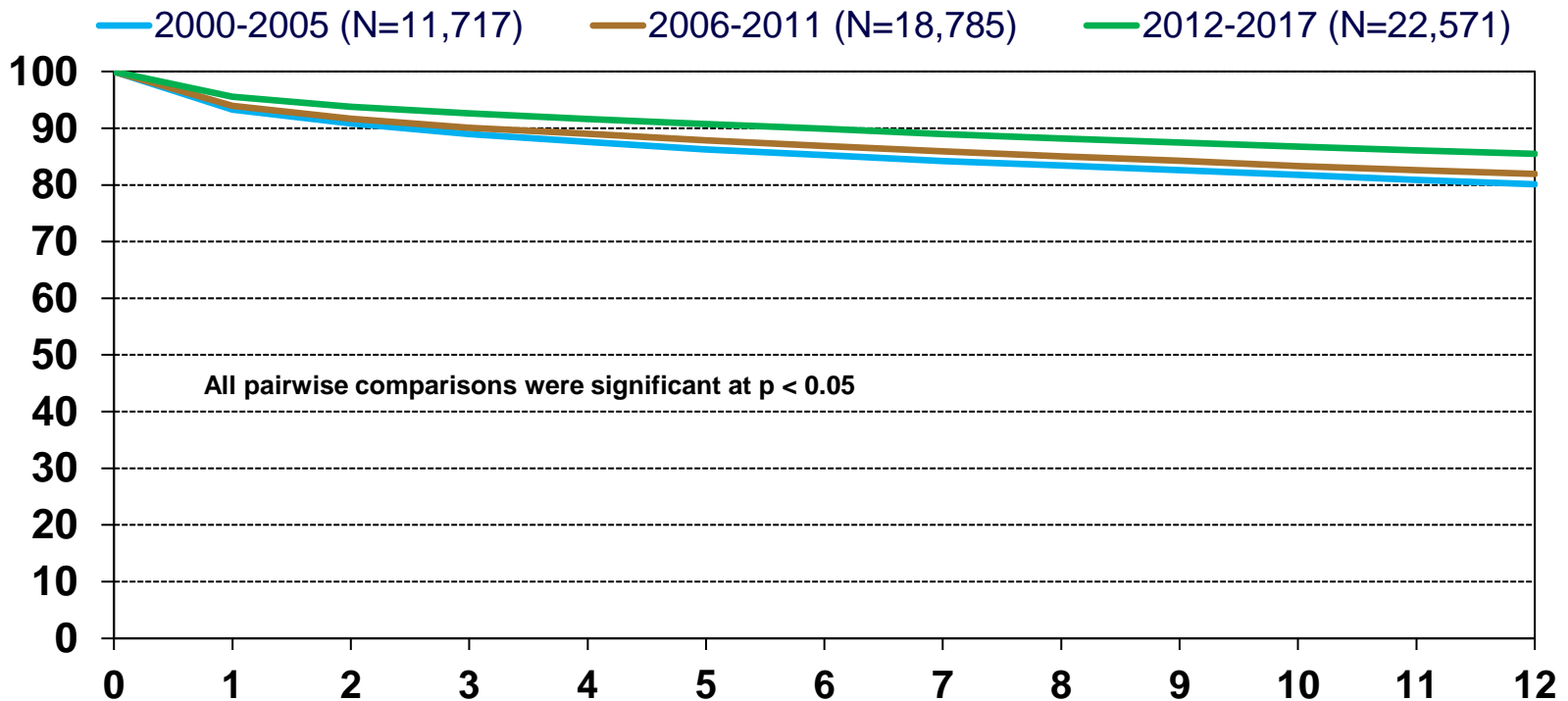
- EMR을 활용한 자동 시스템으로 의료기관 신고율을 높임
- EMR 시스템 인증기준 중 기능성 부분 내 공공정보 연계 부분에 필수 항목으로 추가돼 2024년 인증기준부터 적용될 예정

통보 절차	뇌사추정자 기준	발생 통보 창																		
<pre> graph TD A(뇌사추정자 발생) --> B[의심조건 확인(전산)] B --> C{주치의 확인} C -- 뇌사 아님 --> B C -- 통보 --> D[KODA 출동 (일반/긴급)] </pre>	<p>○ 증환자실 기록지에 입력된 정보가 뇌사추정자 기준에 해당하는 경우(6시간 지속)</p> <p>- 뇌사추정자 기준은 병원과 논의하여 최종결정</p> <table border="1" data-bbox="705 933 1224 1315"> <thead> <tr> <th colspan="3">뇌사추정자 기준</th> </tr> <tr> <th>LOC</th> <th>COMA</th> <th>SEDATION</th> </tr> </thead> <tbody> <tr> <td>GCS</td> <td>3점 or 4점</td> <td></td> </tr> <tr> <td>동공반사</td> <td>fixed</td> <td>fixed</td> </tr> <tr> <td>pupil size</td> <td>4mm 이상</td> <td>4mm 이상</td> </tr> <tr> <td>인공호흡기</td> <td>yes</td> <td>yes</td> </tr> </tbody> </table> <p>- 해당 뇌사추정자 기준이 6시간 이상 지속될 것</p>	뇌사추정자 기준			LOC	COMA	SEDATION	GCS	3점 or 4점		동공반사	fixed	fixed	pupil size	4mm 이상	4mm 이상	인공호흡기	yes	yes	
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- Introduction
- Indication of lung transplantation
- Lung allocation system
- **Outcome of lung transplantation**
- Special consideration in ILD patients
- Conclusion

Survival within 12 Months by Era

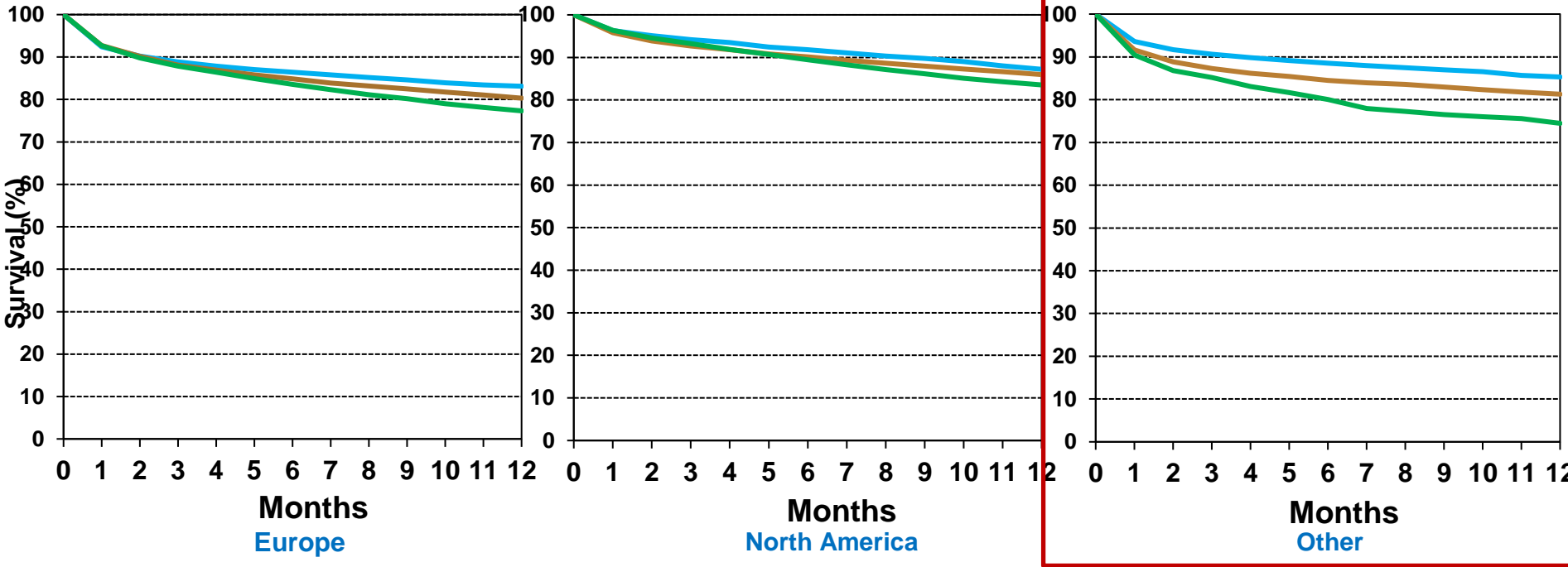
(Transplants: Jan 2000 – Jun 2017)



Survival within 12 M by Location and Recipient Age

(Transplants: Jan 2000 - Jun 2017)

Recipient Age: — 18-39 Years — 40-59 Years — ≥60 Years



Adult Lung Transplants (2000-6/2017)

Statistically Significant Risk Factors For 1-Year Mortality

Recipient age (years) (≥ 56)

Donor age (years) (≥ 40)

PCW (mm/Hg) (≥ 26)

Recipient BMI (kg/m^2) (≥ 25)

Recipient GFR* (mL/min/1.73 m^2) (≤ 95)

Center volume in previous 3 yrs (≤ 100)

Ischemic time (hours) (≥ 5.5)

Recipient bilirubin (mg/dl) (≥ 0.5)

Donor – recipient sex match
(F/M < M/M < F/F)

Donor CMV+/Recipient CMV-

Prior lung surgery

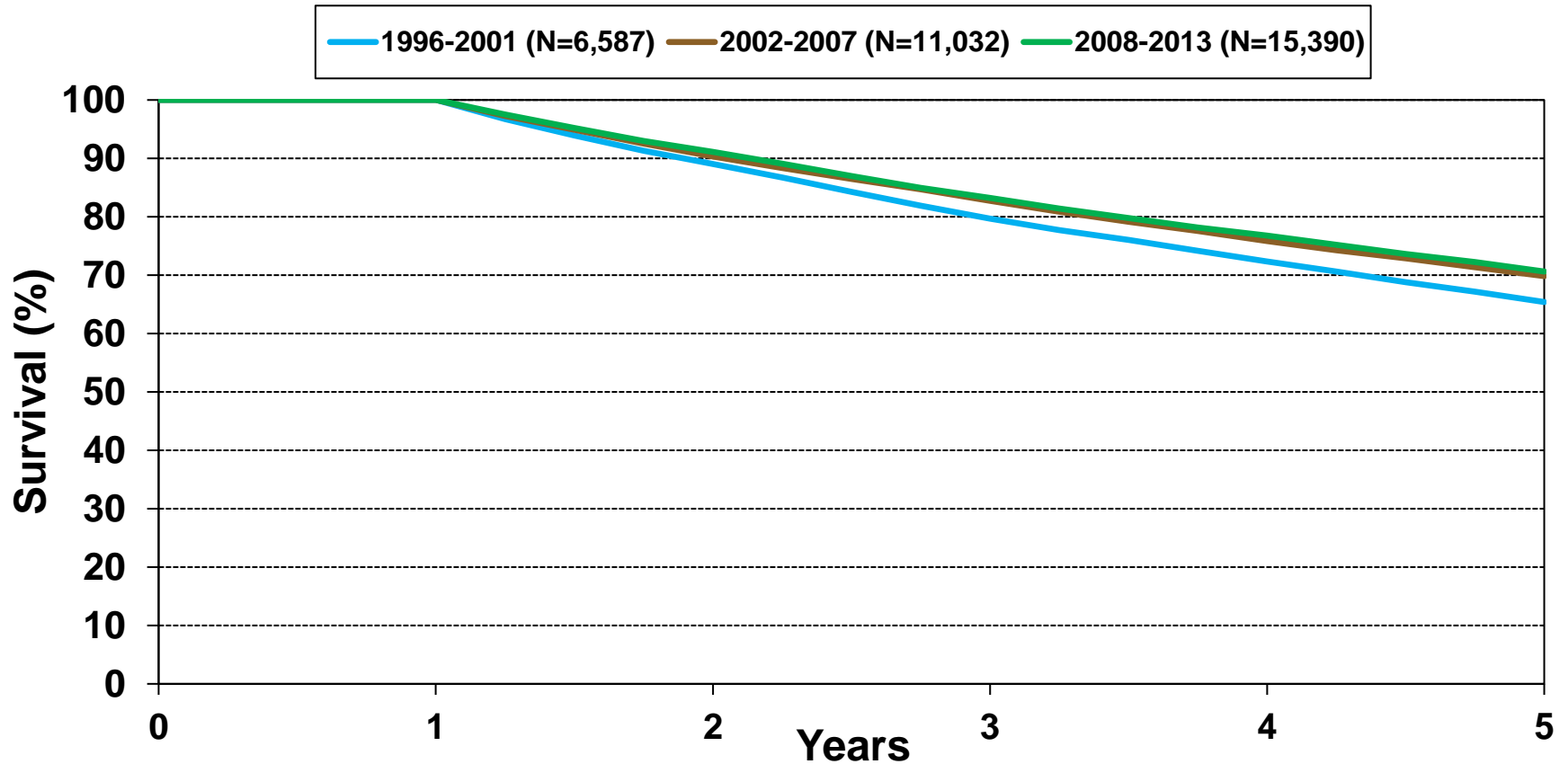
Single lung TPL

MV

Hospitalization

Survival within 5 Years - Conditional on Survival to 1 Year By Era

(Transplants: Jan 1996 - Jun 2013)



Adult Lung Transplants (1996-6/2013)

Statistically Significant Risk Factors For 5-Year Mortality Conditional on Survival to 1 Year

Recipient age (years) (≤ 38 , ≥ 55)

Ischemic time (hours) (≤ 5)

Recipient BMI (kg/m^2) (≥ 24)

Center volume in previous 3 yrs (≤ 80)

Recipient GFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$) (≤ 100)

Donor – recipient sex match
(M/F < M/M < F/F)

Donor CMV+/Recipient CMV-

Prior lung surgery

Single lung TPL

Hospitalization

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Preparing for LTx in patients with ILD

- 1) Transplant referral
- 2) An evaluation period guided by the transplant center
- 3) Active listing by the transplant team
- 4) Concurrent management of disease progression by an experienced ILD team

Criteria for referral and listing for LT in patients with ILD

Timing of referral [#]	Timing of listing
Histopathological UIP	Hospitalisation for respiratory decline, pneumothorax or acute exacerbation
Radiographic probable or definite UIP pattern	Desaturation to <88% on 6MWT or >50 m decline in 6MWD over 6 months
FVC <80% or D_{LCO} <40% pred	Pulmonary hypertension on right heart catheterisation or echocardiography
Relative decline in pulmonary function over the past 2 years: FVC \geq 10% or D_{LCO} \geq 15% or FVC \geq 5% with symptomatic or radiographic progression	Absolute decline in pulmonary function over the past 6 months despite appropriate treatment: FVC >10% or D_{LCO} >10% or FVC >5% with radiographic progression
Any resting or exertional oxygen requirement	
For inflammatory ILDs, disease progression despite treatment	

Common risk factors for adverse post-LTx outcomes in ILD patients

Advanced age

Overweight status

Telomere biology disorders

Prior thoracic surgery

Limited functional status, deconditioning, frailty

Gastro-oesophageal reflux

High-risk atherosclerotic disease

Connective tissue disease manifestations

Corticosteroids, other immunosuppressants

Acute exacerbations

Active mechanical ventilation

Relative risks associated with ILD pharmacotherapies

- **Chronic, high-dose corticosteroids** in particular may increase wound healing complications and risk of anastomotic dehiscence
- Based on potential risks, many LTx programmes consider **maintenance prednisone-equivalent doses >20 mg/day to be a contraindication** (excluding augmented doses for acute exacerbations)
- No data on the impact of other immunomodulating agents on LTx outcomes, but in general it is best **to limit immunosuppressants for ILD to the lowest effective doses** while a patient is listed for transplant

Pre-transplant acute exacerbations

- AE-IPF: in-hospital mortality nearly 50%, 90% in those requiring mechanical ventilation, along with a median survival following AE-IPF of only 3–4 months
- Corticosteroids may be beneficial in some cases including non-IPF ILD, but supportive evidence in AE-IPF is limited
- Transplant in the setting of AE-IPF is associated with worse outcomes
- Patients presenting de novo (without previous evaluation for LTx) represent higher-risk candidates

Outcomes and considerations after LTx for ILD

- ISHLT registry data: among ILD recipients surviving >5 years, ~25% of deaths are due to malignancy including lymphoma, and nearly 7% are due to cardiovascular causes
- Coronary artery disease: IPF, SLE, RA
- Gastrointestinal disease
 - GER - antireflux surgery, medication
 - GI dysmotility

Other consideration

- Pulmonary hypertension with RV dysfunction
- Deconditioning → active rehab!
- Close communication with lung transplant team

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Conclusion

- Lung transplantation: only treatment modality for end-stage lung disease patients
- Relatively short survival compared to other organs d/t high immunogenicity of lungs and risk of infection
- Severe shortage of donor lungs and high mortality on waiting list in Korea

Conclusion

- Specific consideration in ILD patients
 - ✓ Timely referral and listing for TPL
 - UIP/inflammatory myositis
 - ✓ Evaluation of GERD/esophageal dysmotility
 - ✓ Immunosuppressant agents
 - ✓ Acute exacerbation – high risk



Thank you for your attention