Limbs, Lungs and Guts in MND

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Prognosis

Average survival 30-36 months from symptom onset

(18-24 months from diagnosis).

50% dead at 30 months from onset

10-20% live $\geq$ 5yrs

5-10% live $\geq$ 10yrs

V. occasional patients live 20 yrs (or more)

Disease Progression

- onset mid 50's to mid 70's (av. 63yrs)
- typically fit and with little co-morbidity
- patients progress from fit and active to high levels of dependency over 2-3yrs
- houses converted into mini-hospitals, families and partners into carers/nurses
- High proportion (~50%) have cognitive impairment, with resultant emotional blunting, further eroding loving relationships

Causation or Association?

- **Causation** is the science of inferring the presence and magnitude of a cause/effect relationship from data.

- When two variables are related, we say that there is **association** between them, e.g. poor socio-economic background and obesity – socio-economic background itself does not cause obesity but the restrictions in places on diet and exercise etc do!

Causation or Association?

- A study finds a relationship between paternal silk tie ownership and infant mortality.
- On the back of this, the government implements a programme in which 5 silk ties are given to all men aged 18–45 with a view to reducing infant mortality.
- This is madness! We all understand the difference between association and causation!

Disease Progression

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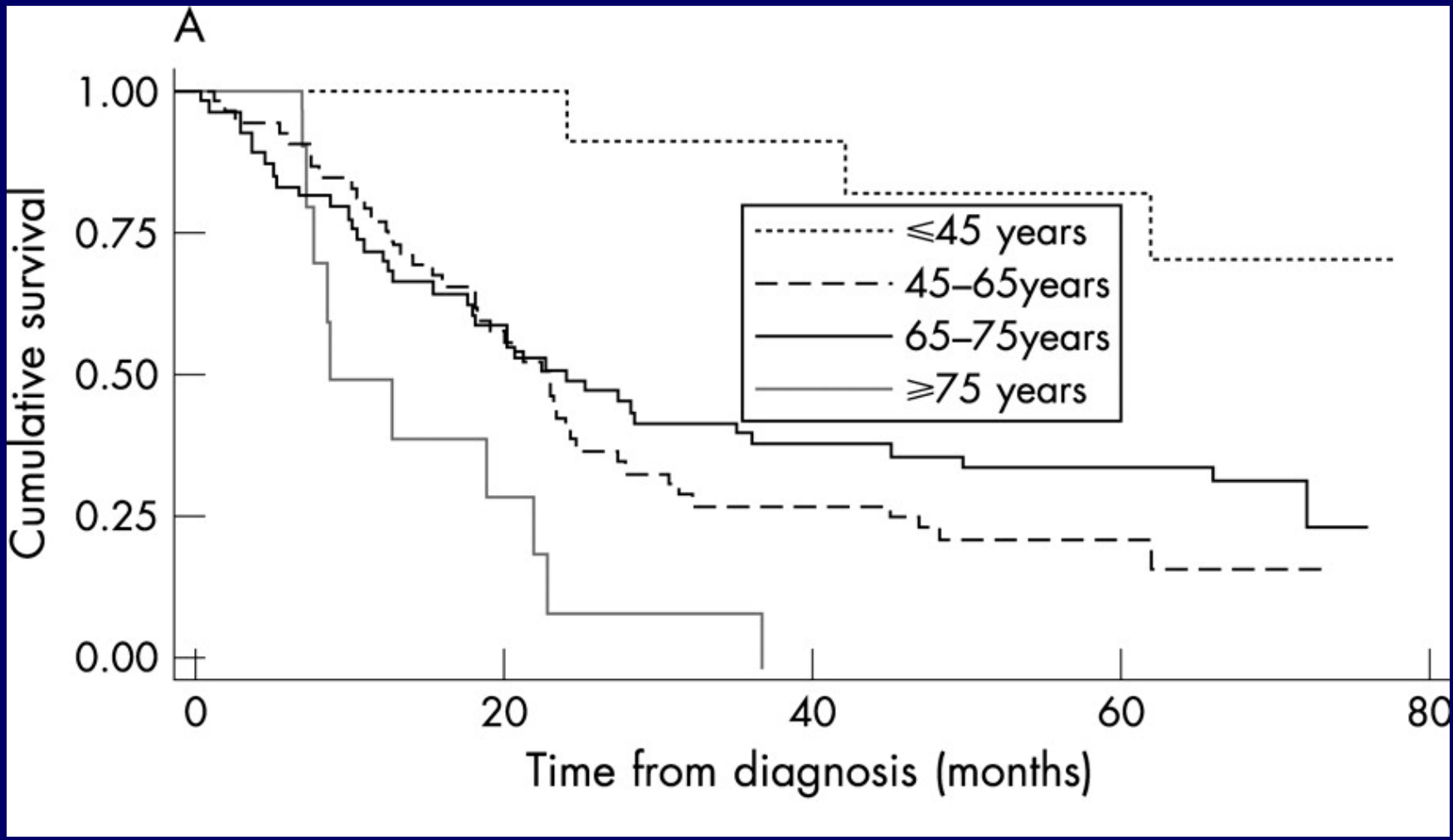
What Predicts Prognosis?

1. Age

Age



Zoccolella S et al. J Neurol Neurosurg Psychiatry 2008;79:33-37

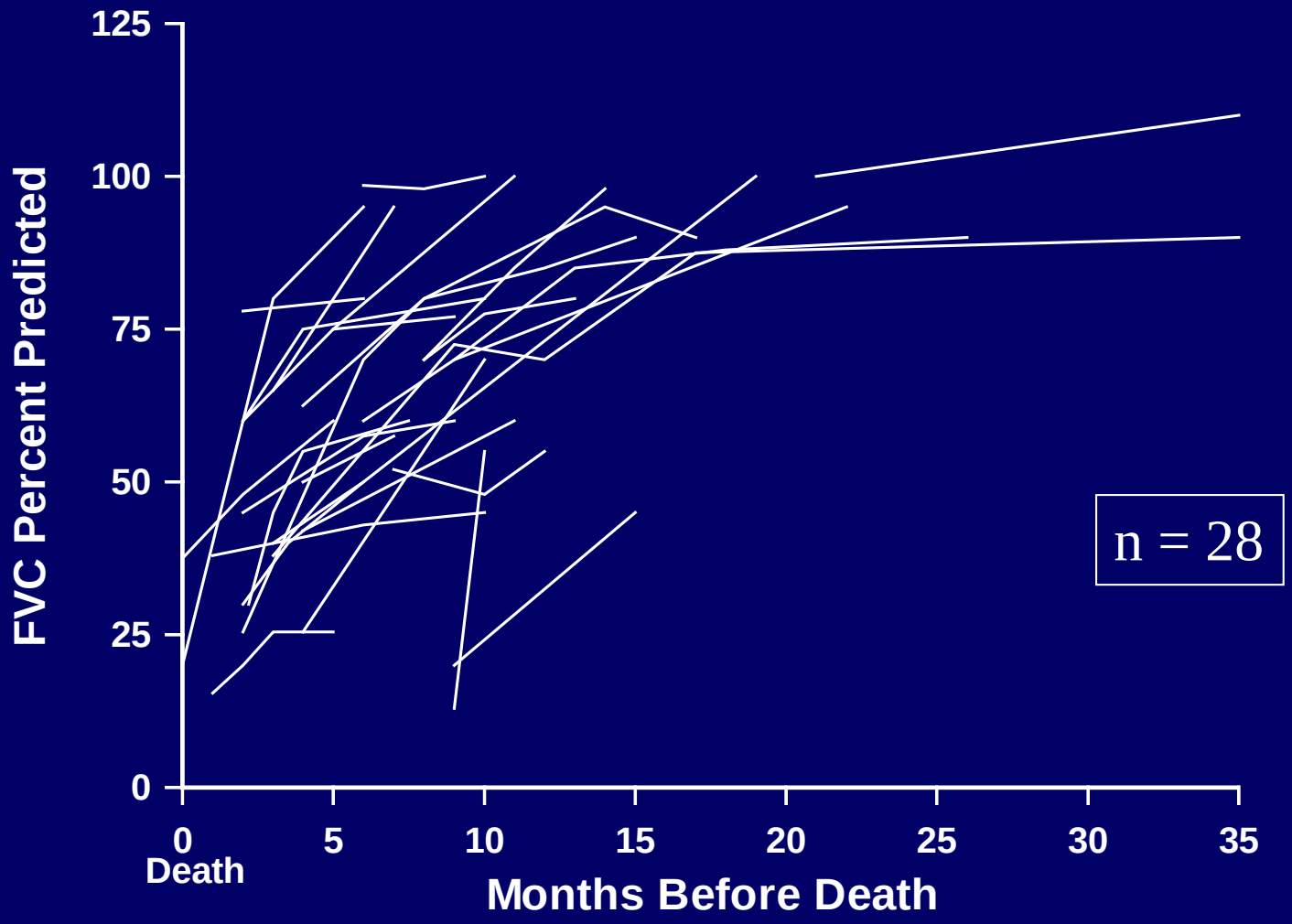
What Predicts Prognosis?

1. Age
2. Respiratory function (“Lungs”)

Respiratory Function in MND

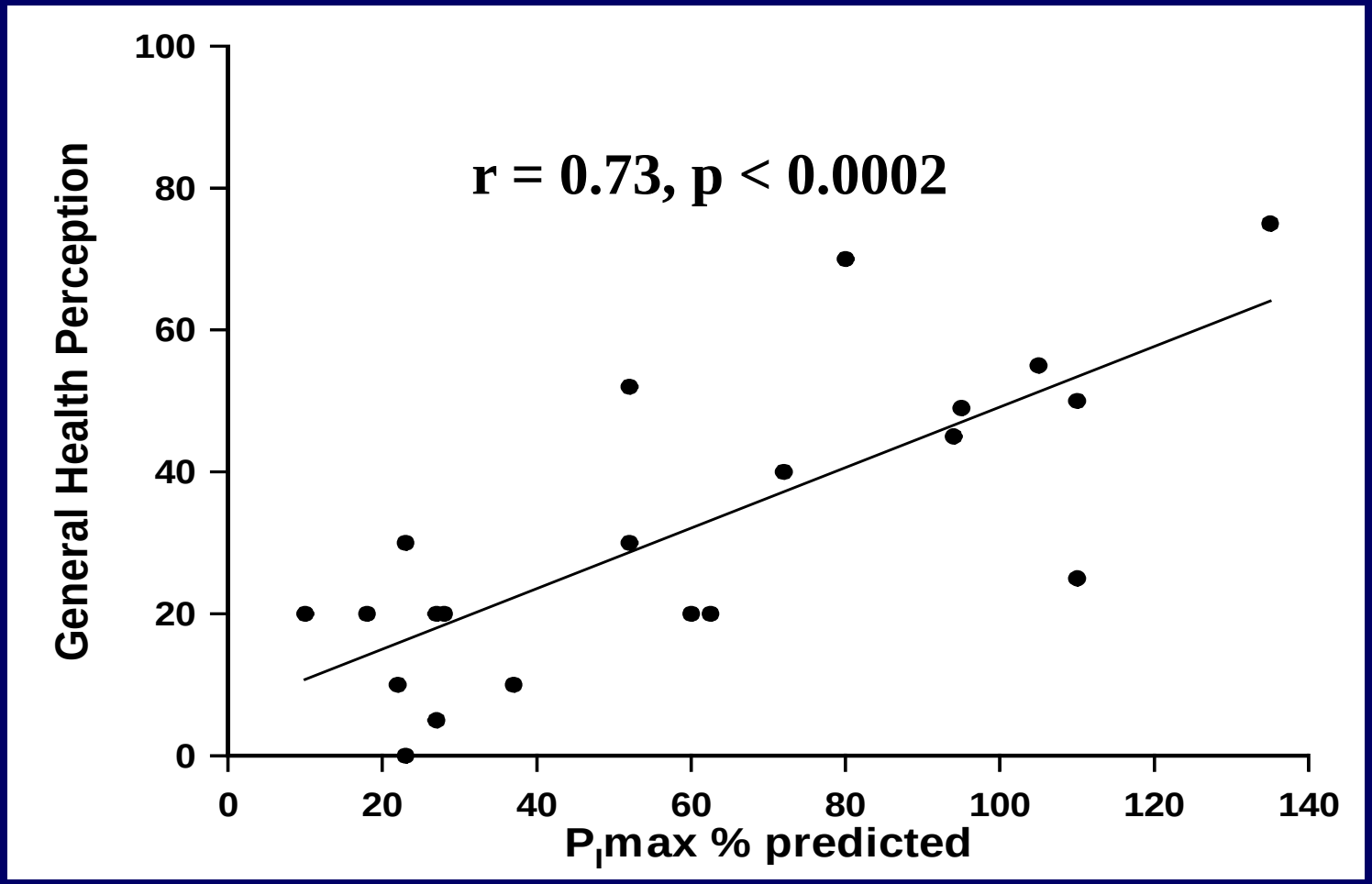
- Respiratory muscle weakness universal with respiratory failure all but universal mode of death.
- Mediates an effect not just on survival, but also on quality of life.

FVC and Survival



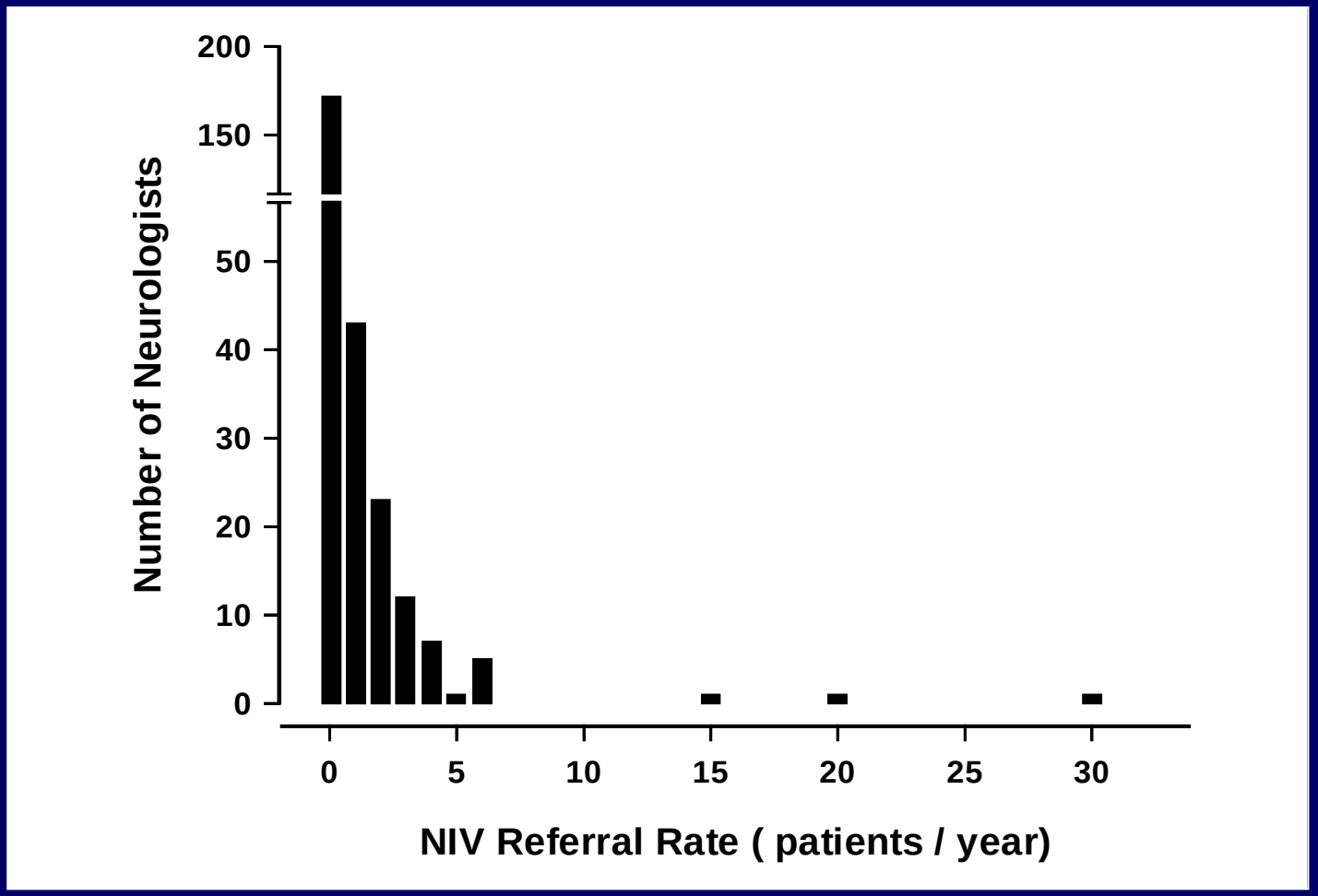
Fallat, Arch Neurol, 1979

QoL vrs Respiratory Function



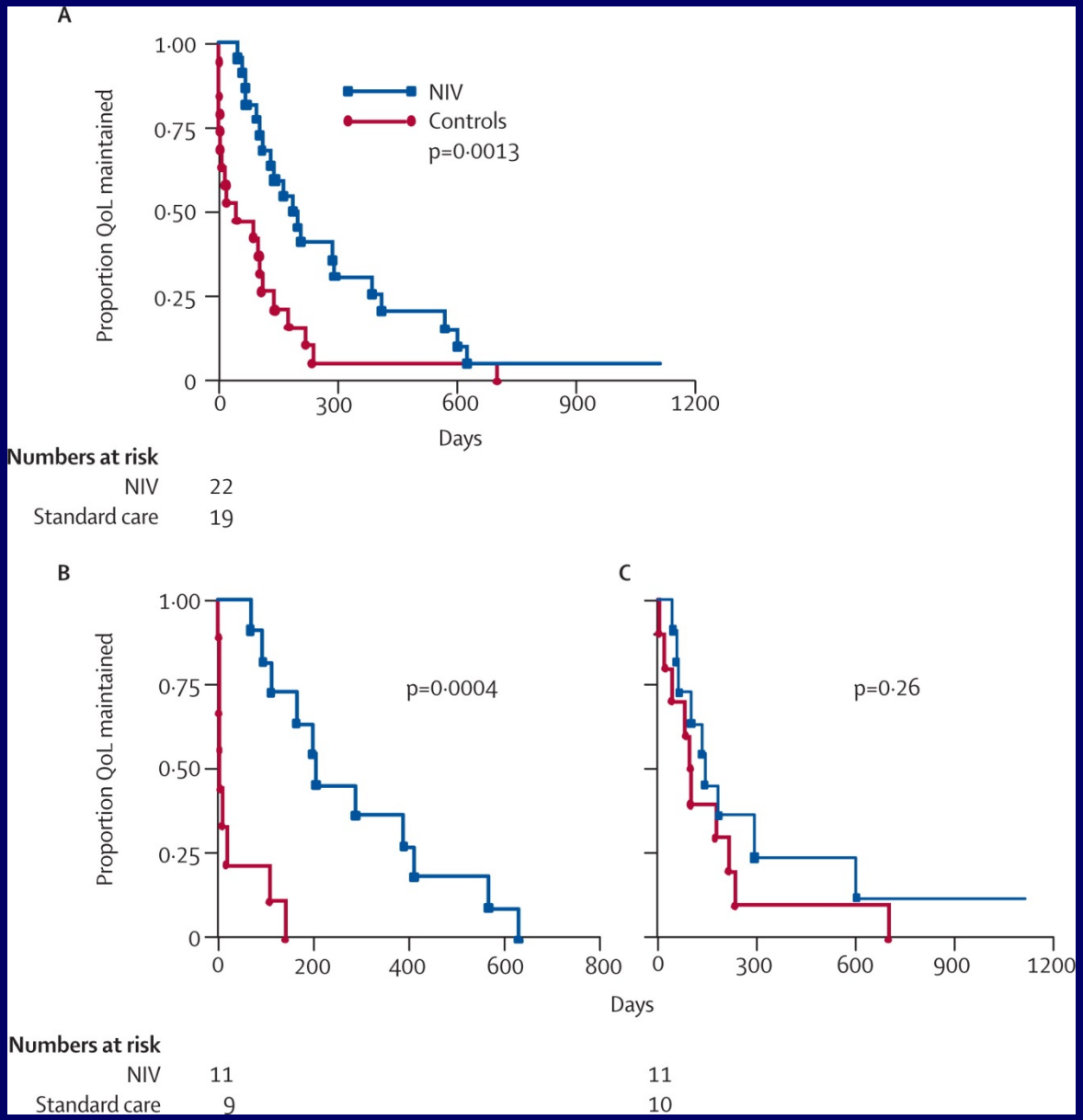
Bourke *et al*, Neurology, 2001

UK Clinical Practice, 2000

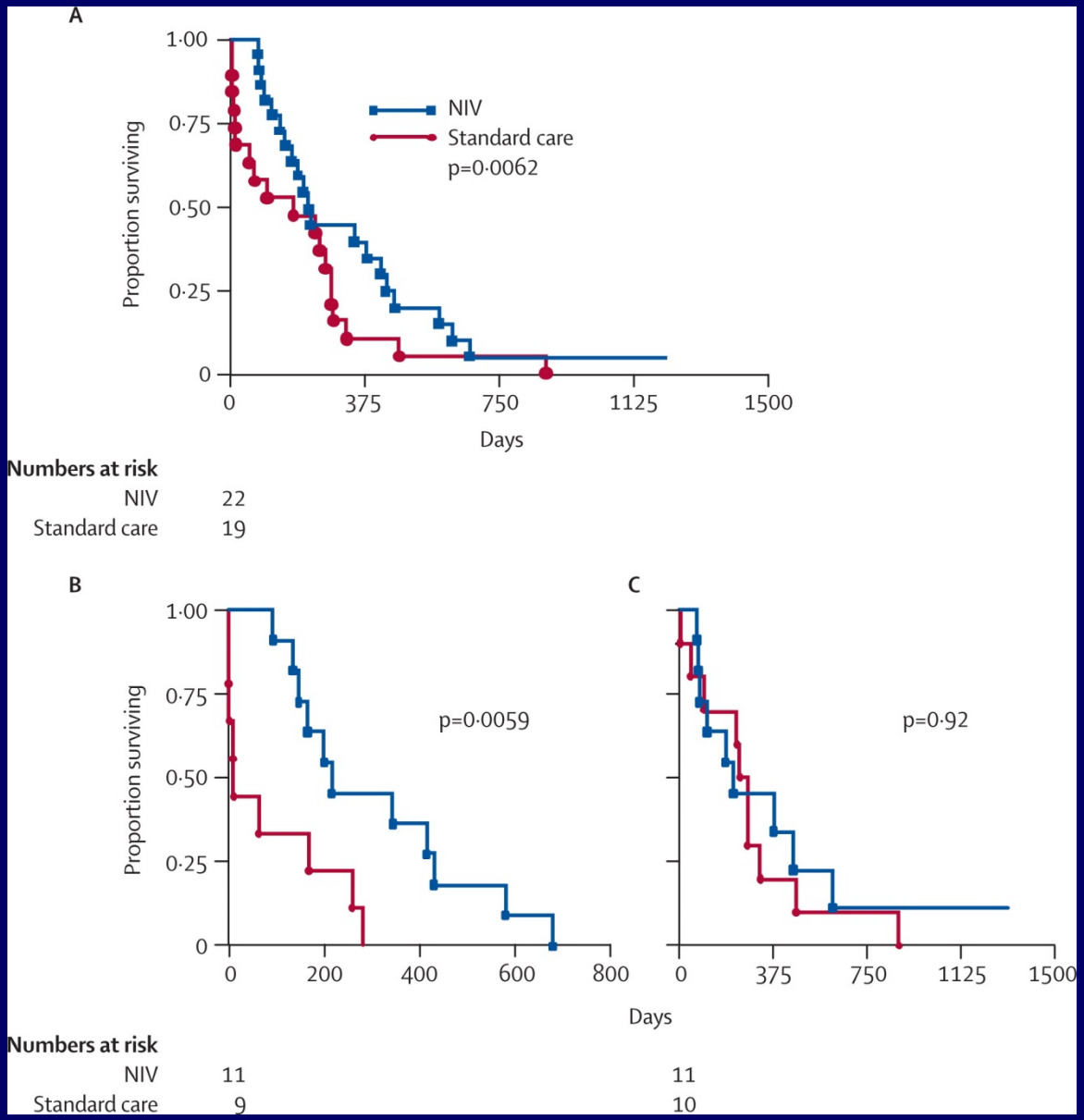


Bourke *et al*, ALS Other Motor Neuron Disord, 2002

QoL Above 75% of Baseline



Survival from Randomisation



Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial

Stephen C Bourke, Mark Tomlinson, Tim L Williams, Robert E Bullock, Pamela J Shaw, G John Gibson

Lancet Neurol 2006; 5: 140–47

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Summary

Background Few patients with amyotrophic lateral sclerosis currently receive non-invasive ventilation (NIV), reflecting clinical uncertainty about the role of this intervention. We aimed to assess the effect of NIV on quality of life and survival in amyotrophic lateral sclerosis in a randomised controlled trial.

Methods 92 of 102 eligible patients participated. They were assessed every 2 months and randomly assigned to NIV (n=22) or standard care (n=19) when they developed either orthopnoea with maximum inspiratory pressure less than 60% of that predicted or symptomatic hypercapnia. Primary validated quality-of-life outcome measures were the short form 36 mental component summary (MCS) and the sleep apnoea quality-of-life index symptoms domain (sym). Both time maintained above 75% of baseline (T_{μ}MCS and T_{μ}sym) and mean improvement (μMCS and μsym) were measured.

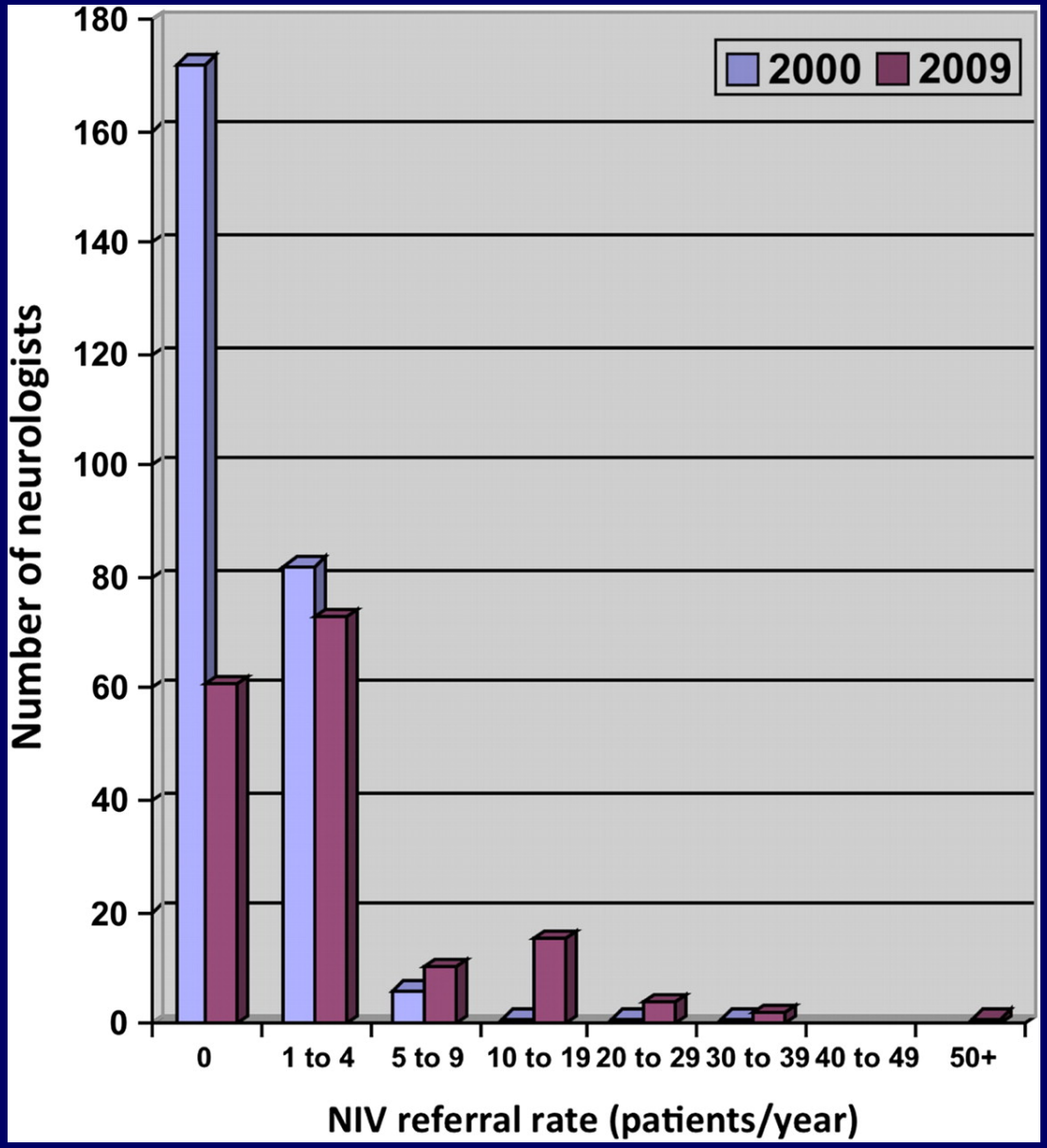
Findings NIV improved T_{μ}MCS, T_{μ}sym, μMCS, μsym, and survival in all patients and in the subgroup with better bulbar function (n=20). This subgroup showed improvement in several measures of quality of life and a median survival benefit of 205 days (p=0·006) with maintained quality of life for most of this period. NIV improved some quality-of-life indices in those with poor bulbar function, including μsym (p=0·018), but conferred no survival benefit.

Interpretation In patients with amyotrophic lateral sclerosis without severe bulbar dysfunction, NIV improves survival with maintenance of, and improvement in, quality of life. The survival benefit from NIV in this group is much greater than that from currently available neuroprotective therapy. In patients with severe bulbar impairment, NIV improves sleep-related symptoms, but is unlikely to confer a large survival advantage.

Conclusions of RCT

- Significant overall sustained improvement in QoL.
- Survival benefit of ~ 7 months (twice that seen with Riluzole).
- All survival benefit seen in “better” bulbar function group.

NIV Referral Practice



O'Neill C L *et al*. JNNP 2011

Prevalence of NIV and Tracheostomy Ventilation in MND

	Japan	United States	Europe (UK, Italy, Denmark and Sweden)
Non-invasive ventilation, range (%)	7–46	19–87	3–44
Tracheostomy ventilation, range (%)	29–38	4	1–31

Turner *et al*, 2019

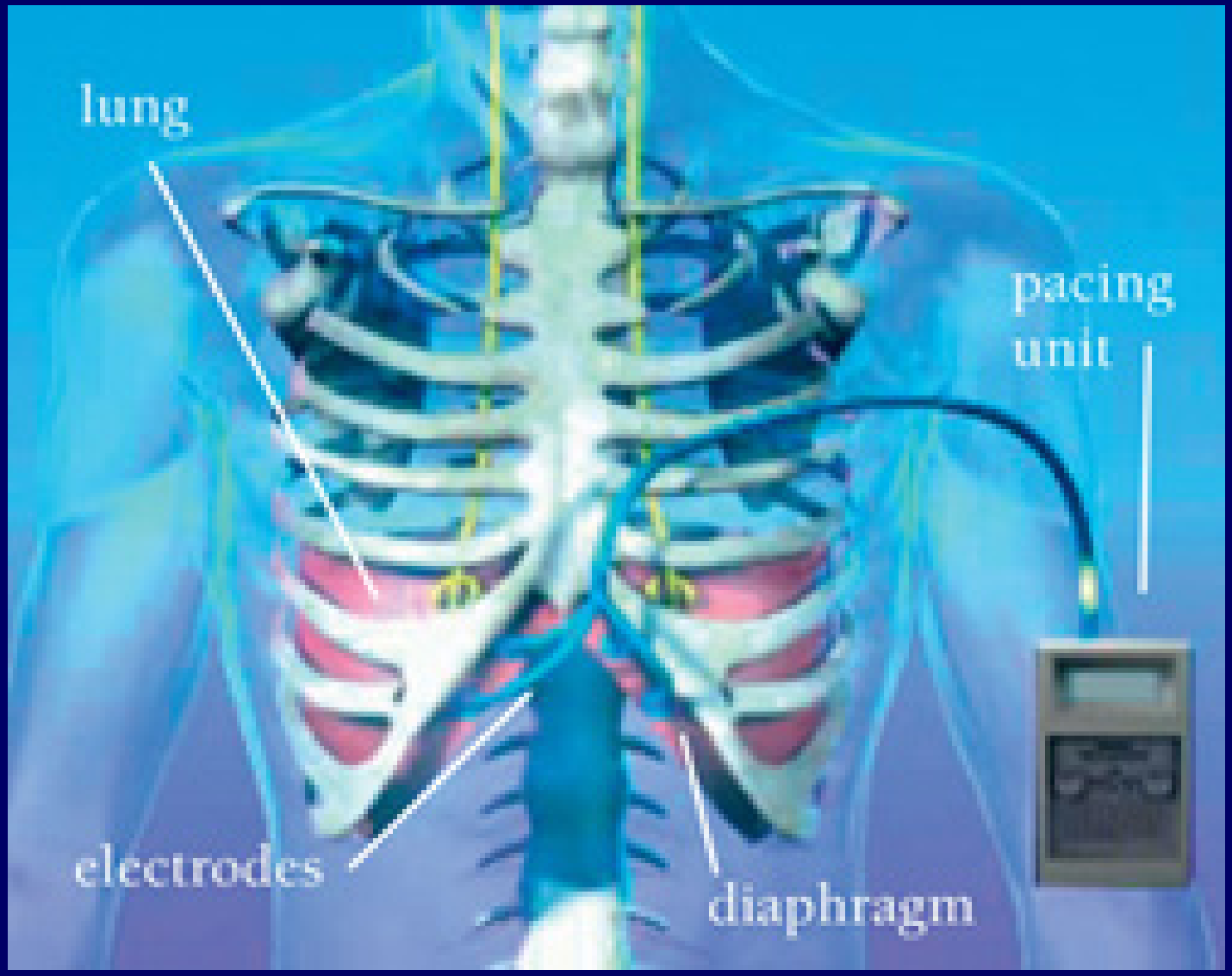
Tracheostomy Ventilation in MND?

- Is tracheostomy appropriate in MND patients?
- If so who for?
- When should it be withdrawn?
- Care cost and impact?
- Late evolution or emergence og cogntive issues

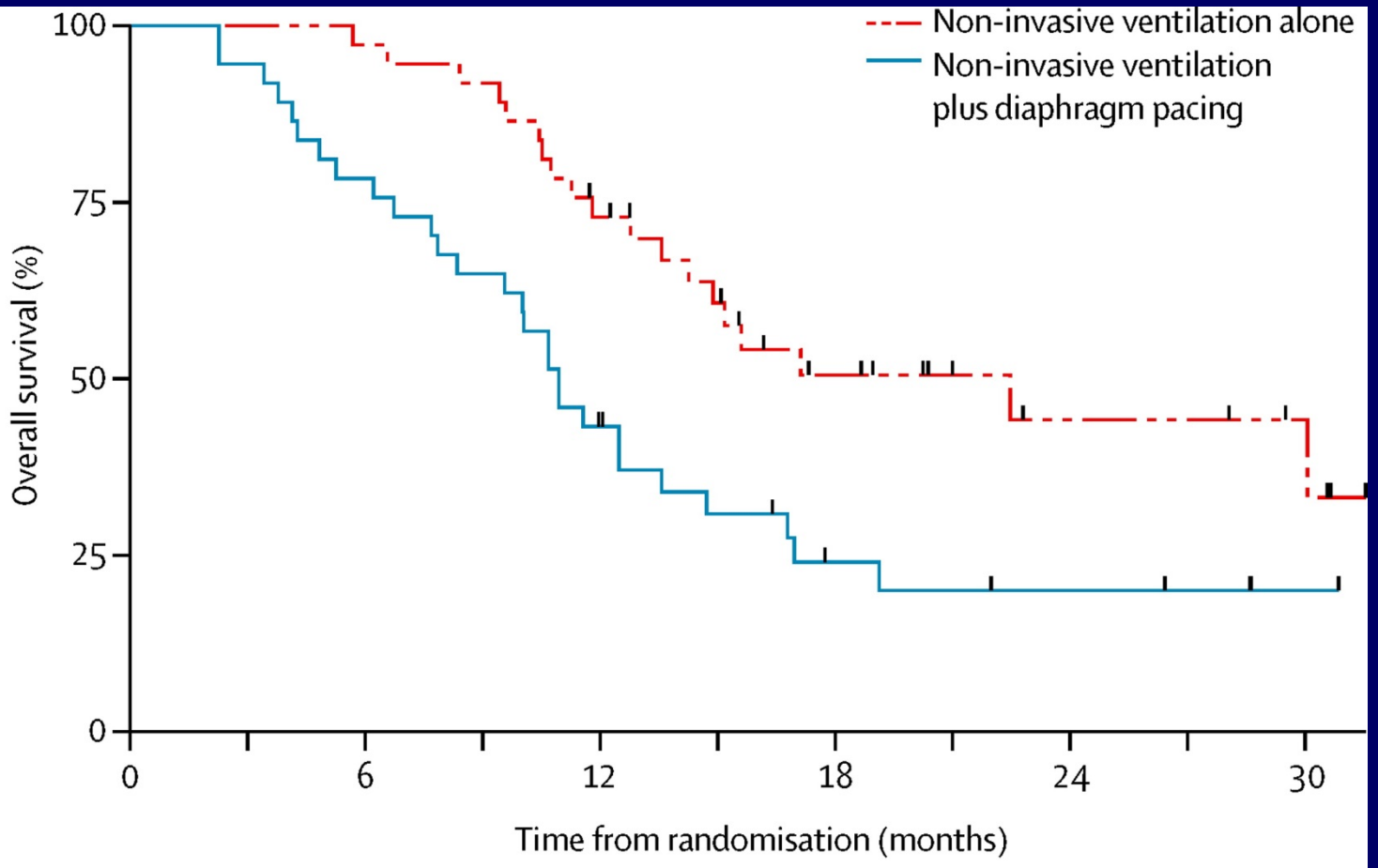
Local Experience of Invasive Trachy Ventilation (IV):

- Currently fewer than 10% of UK MND patients undergo IV.
- Local (Newcastle) crude data: mean 32-36 months survival post-tracheostomy (N=14).
- Concerns re: communication and becoming “locked-in”
- Care package > £250K pa!

Diaphragm Pacing



DiPALS Overall Survival



Number at risk						
Non-invasive ventilation	37	36	26	13	6	4
Non-invasive ventilation plus diaphragm pacing	37	29	14	6	4	1

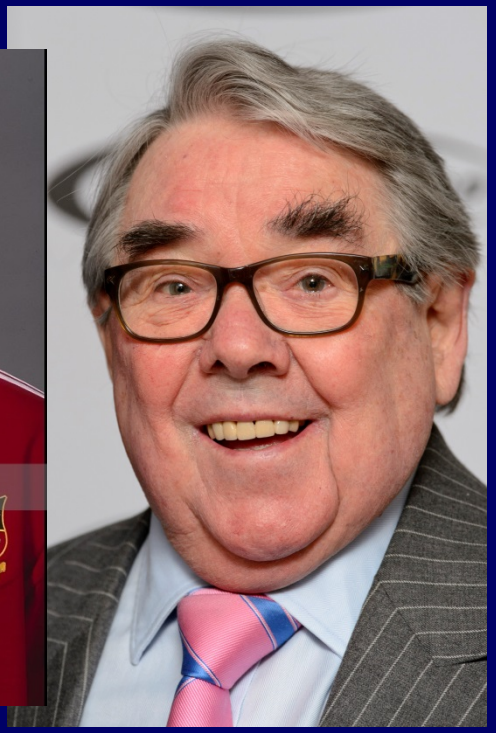
Ventilatory Support and MND

1. For symptoms not survival (or poor tests of respiratory function)
2. Not for all
3. Pros and cons must be discussed in detail
4. Not for simply for those with advanced physical disability at the end of their disease course

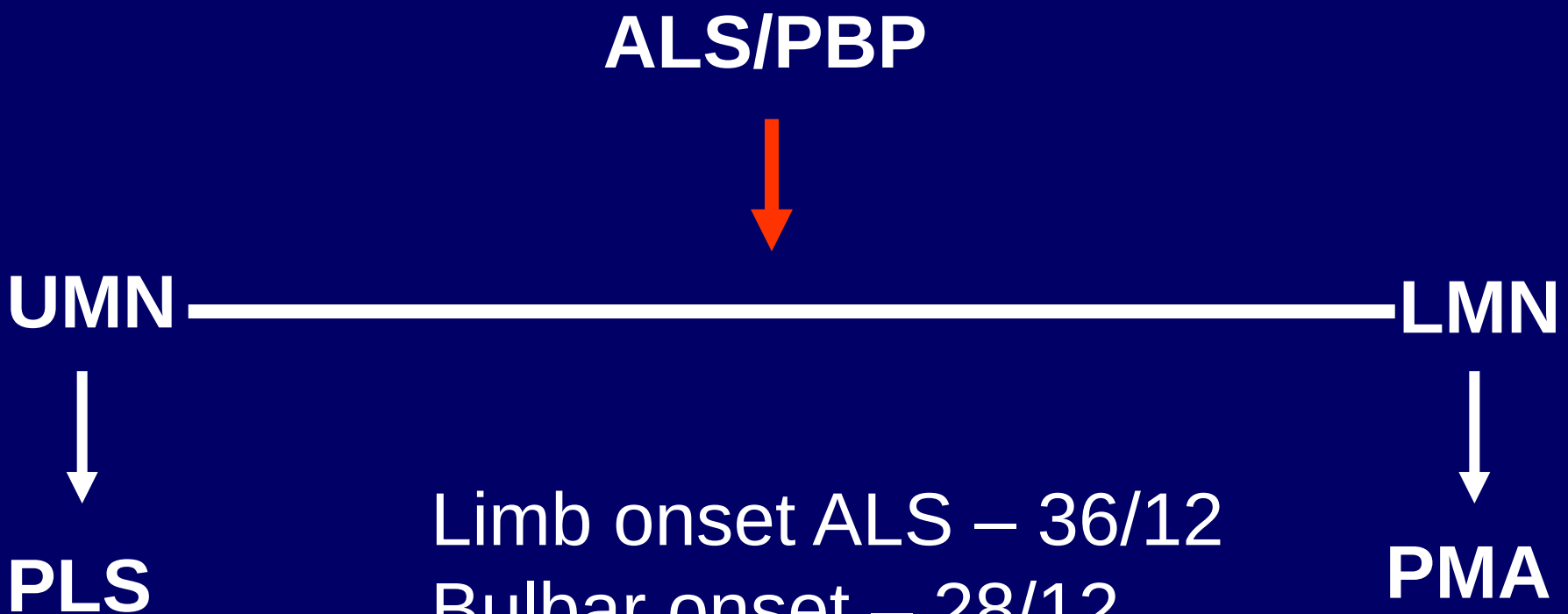
What Predicts Prognosis?

1. Age
2. Respiratory function
3. Disease phenotype (“Limbs”)

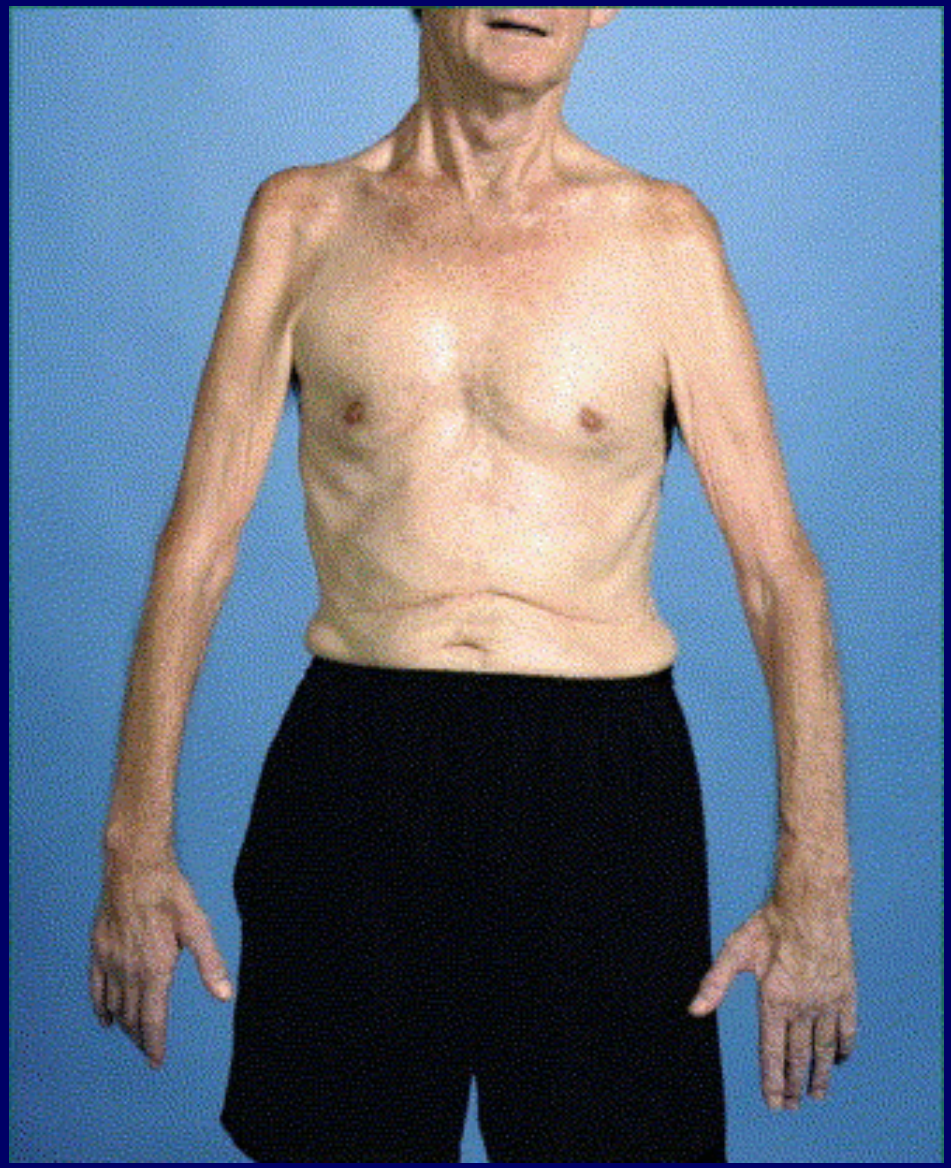

adidas
SCOTTISH
PROVIDENT



Disease Phenotype

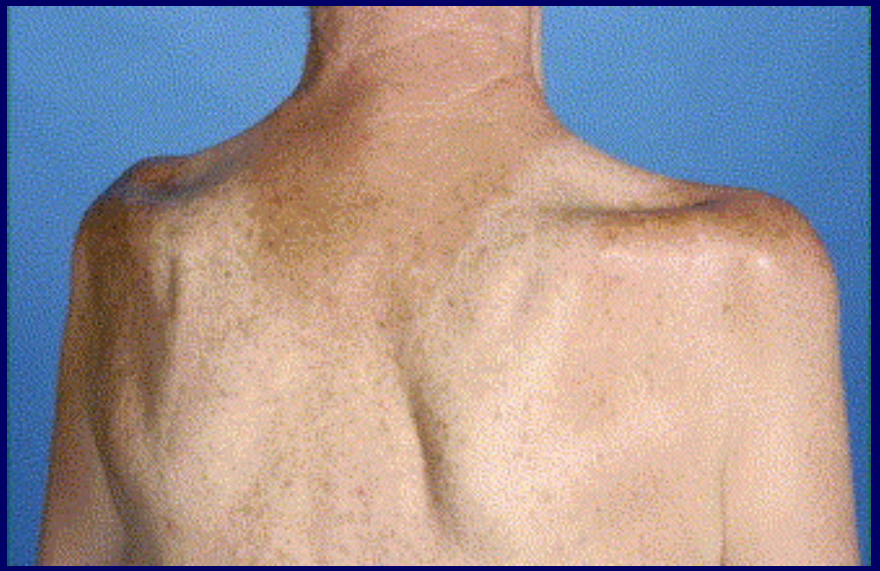


The Flail-Arm Variant

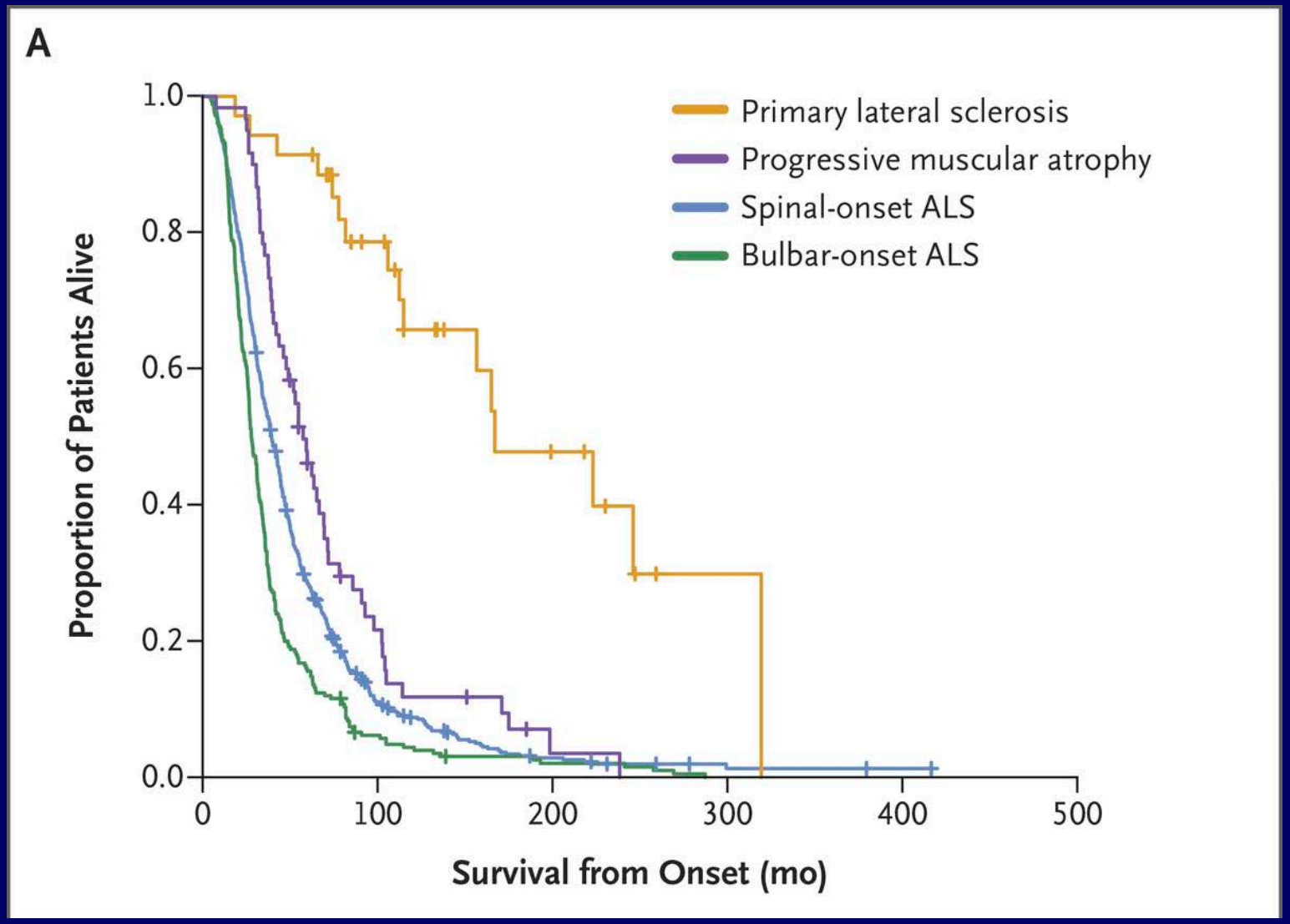


Average survival 5yrs

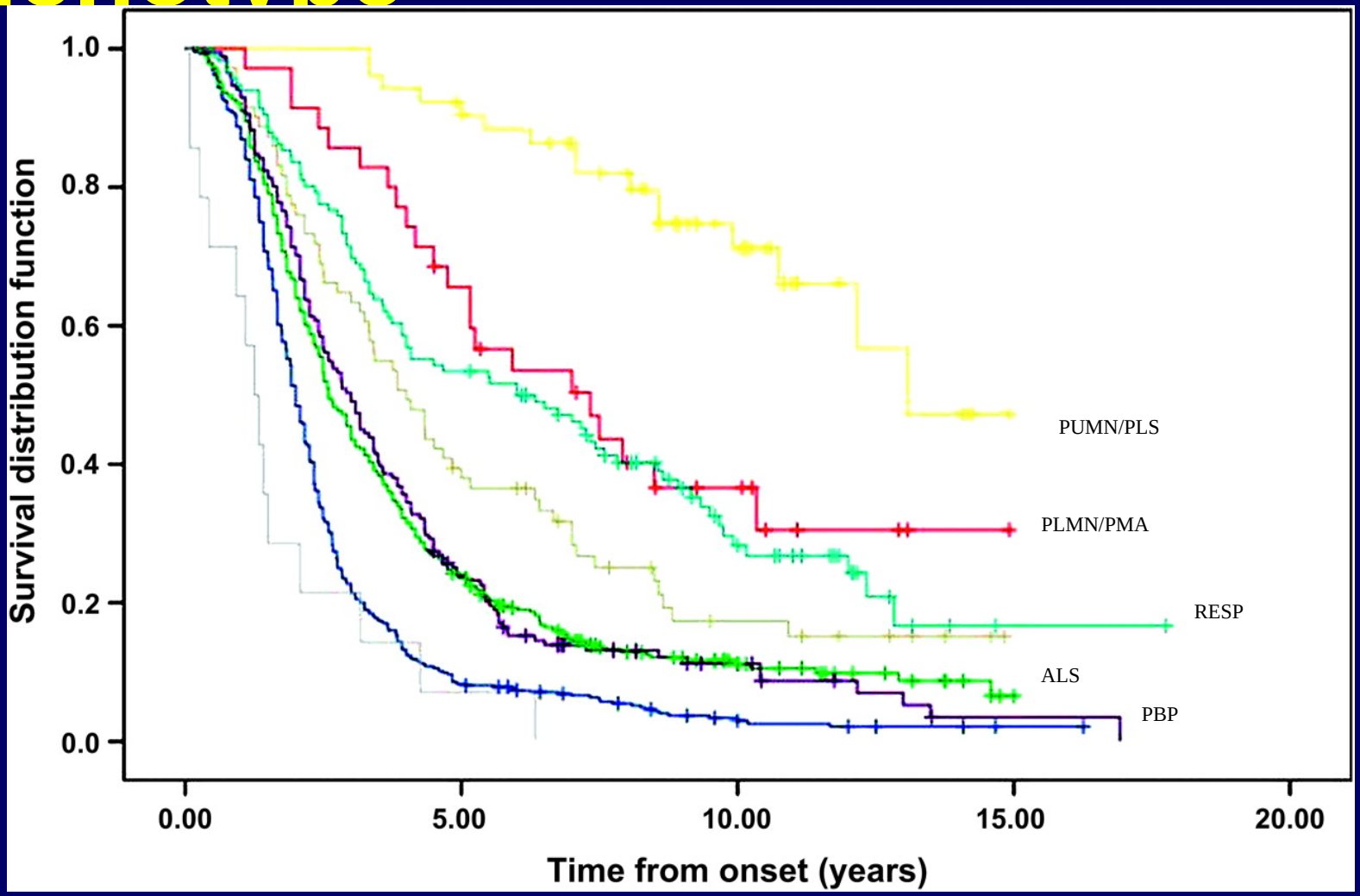
M:F ratio 6:1 (1.7:1)



MND Phenotype



Tracheostomy Free Survival by Phenotype



Chiò A et al. J Neurol Neurosurg Psychiatry 2011;82:740-746

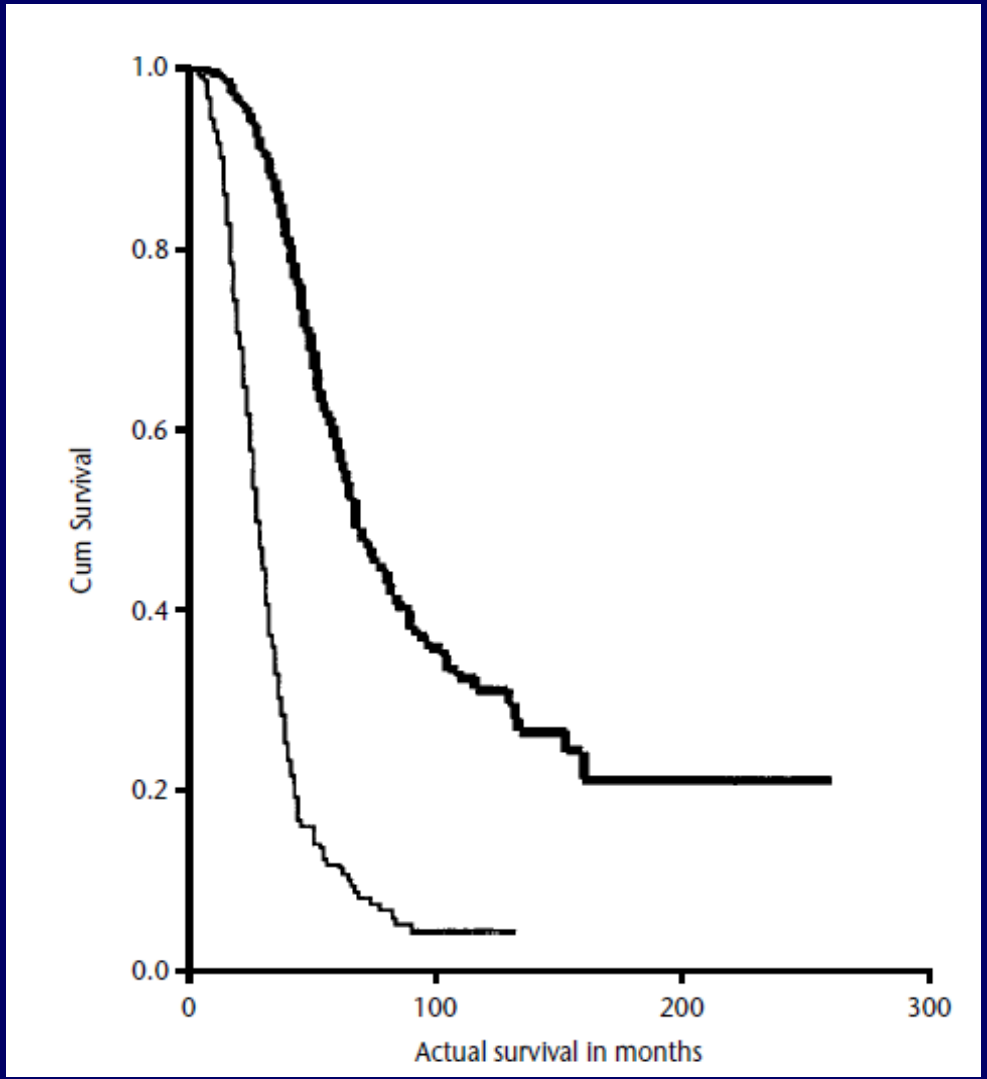
What Predicts Prognosis?

1. Age
2. Respiratory function
3. Disease phenotype
4. Delay to diagnosis

Time to Diagnosis

Thick Black >6 months

Thin Black <6 months

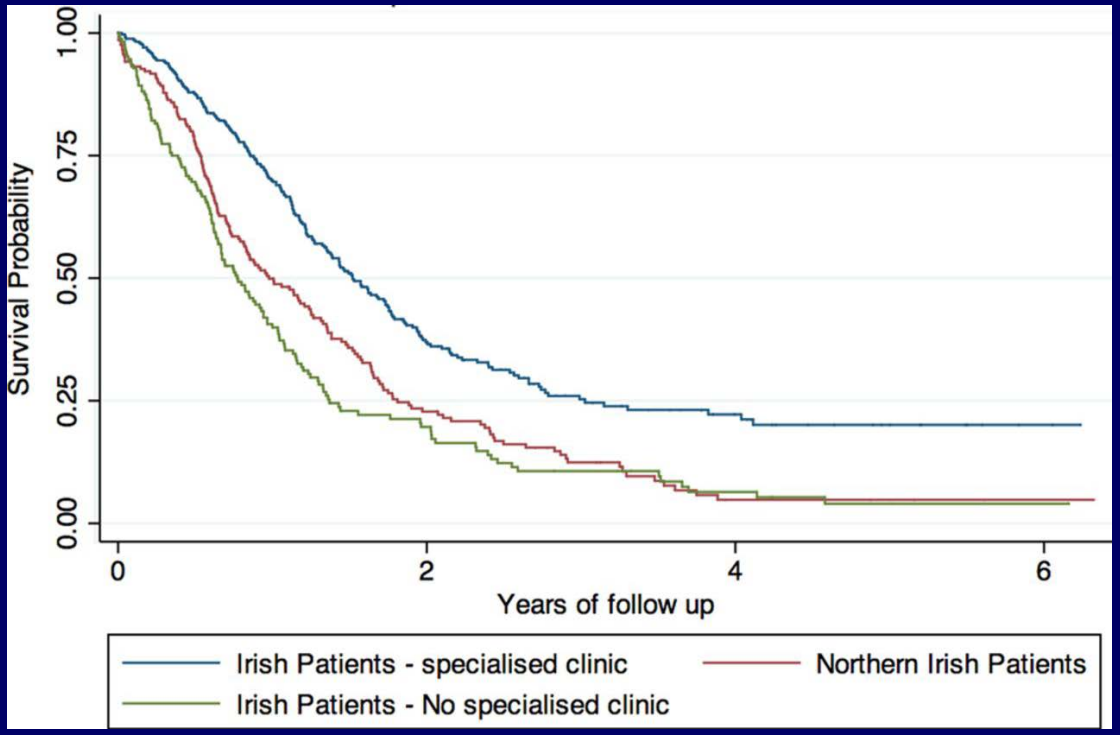


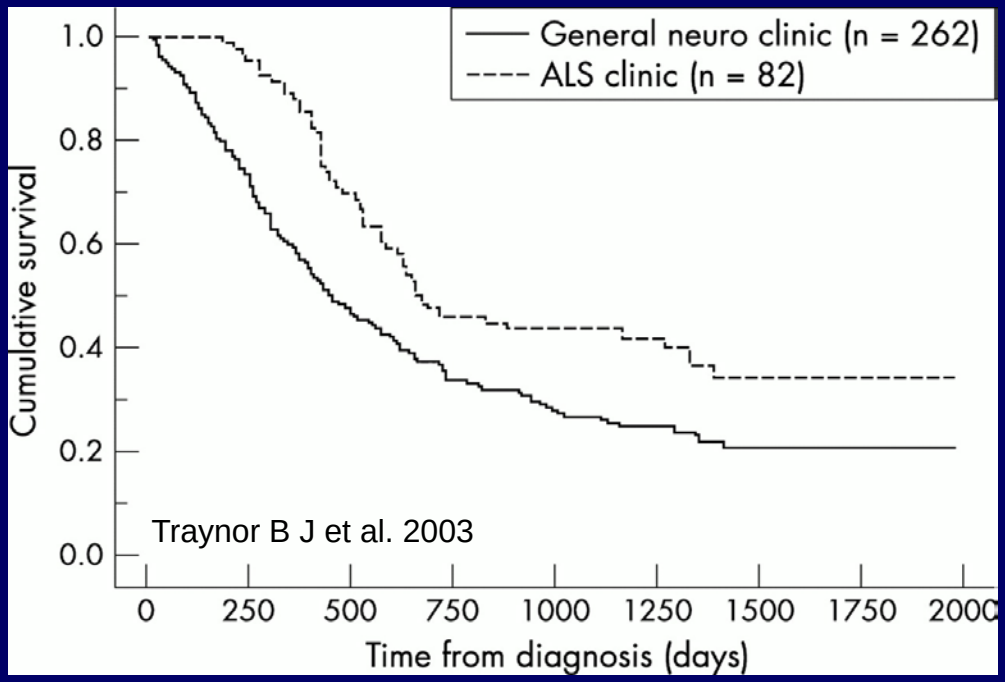
Turner *et al* 2002, ALS & FTD

What Predicts Prognosis?

1. Age
2. Respiratory function
3. Disease phenotype
4. Delay to diagnosis
5. Multidisciplinary MND Clinic

MND MDT clinic





Weight Loss and Nutritional "Failure"

- Nutritional failure/weight loss and/or difficulty maintaining weight, hydration and medication intake common.
- Weight loss inevitable as muscle mass lost (often early in disease course), appetite diminishes, eating becomes slower and more difficult and metabolic rate increases.

HighCALS

- Exploration and trial of the effect of high calorie dietary interventions for MND (ALS) patients.
- Preliminary stage exploring HCPs attitudes and experiences of dietary supplements in MND
- Technically likely to be extremely difficult to control and monitor – may ultimately be observational rather than interventional?

Gastrostomy in MND

- Issues abound regarding timing of gastrostomy and insertion technique
- Benefits considered in the main to be ease of parenteral administration of nutrition, fluid & medication with benefit for QoL?
- No or little impact on survival

PROGAS

Prospective cohort study of gastrostomy in MND looking at technique, nutrition and survival.

Outcomes:

- 30 day mortality
- Complication rates at up to 90 days
- Survival from gastrostomy
- Nutritional status
- Self perceived QoL
- Carer strain.

Gastrostomy in patients with amyotrophic lateral sclerosis (ProGas): a prospective cohort study

*ProGas Study Group**

Lancet Neurol 2015; 14: 702–09

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See Comment page 671

*Members listed in the appendix

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See Online for appendix

Summary

Background Gastrostomy feeding is commonly used to support patients with amyotrophic lateral sclerosis who develop severe dysphagia. Although recommended by both the American Academy of Neurology and the European Federation of Neurological Societies, currently little evidence indicates the optimum method and timing for gastrostomy insertion. We aimed to compare gastrostomy insertion approaches in terms of safety and clinical outcomes.

Methods In this large, longitudinal, prospective cohort study (ProGas), we enrolled patients with a diagnosis of definite, probable, laboratory supported, or possible amyotrophic lateral sclerosis who had agreed with their treating clinicians to undergo gastrostomy at 24 motor neuron disease care centres or clinics in the UK. The primary outcome was 30-day mortality after gastrostomy. This study was registered on the UK Clinical Research Network database, identification number 9923.

Findings Between Nov 2, 2010, and Jan 31, 2014, 345 patients were recruited of whom 330 had gastrostomy. 163 (49%) patients underwent percutaneous endoscopic gastrostomy, 121 (37%) underwent radiologically inserted gastrostomy, 43 (13%) underwent per-oral image-guided gastrostomy, and three (1%) underwent surgical gastrostomy. 12 patients (4%, 95% CI 2·1–6·2) died within the first 30 days after gastrostomy: five (3%) of 163 after percutaneous endoscopic gastrostomy, four (3%) of 121 after radiologically inserted gastrostomy, and three (7%) of 43 after per-oral image-guided gastrostomy (p=0·46). Including repeat attempts in 14 patients, 21 (6%) of 344 gastrostomy procedures could not be completed: 11 (6%) of 171 percutaneous endoscopic gastrostomies, seven (6%) of 121 radiologically inserted gastrostomies, and three (6%) of 45 per-oral image-guided gastrostomies (p=0·947).

Interpretation The three methods of gastrostomy seemed to be as safe as each other in relation to survival and procedural complications. In the absence of data from randomised trials, our findings could inform clinicians and patients in reaching decisions about gastrostomy and will stimulate further research into the nutritional management in patients with amyotrophic lateral sclerosis.

PROGAS

Prospective cohort study of gastrostomy in MND:

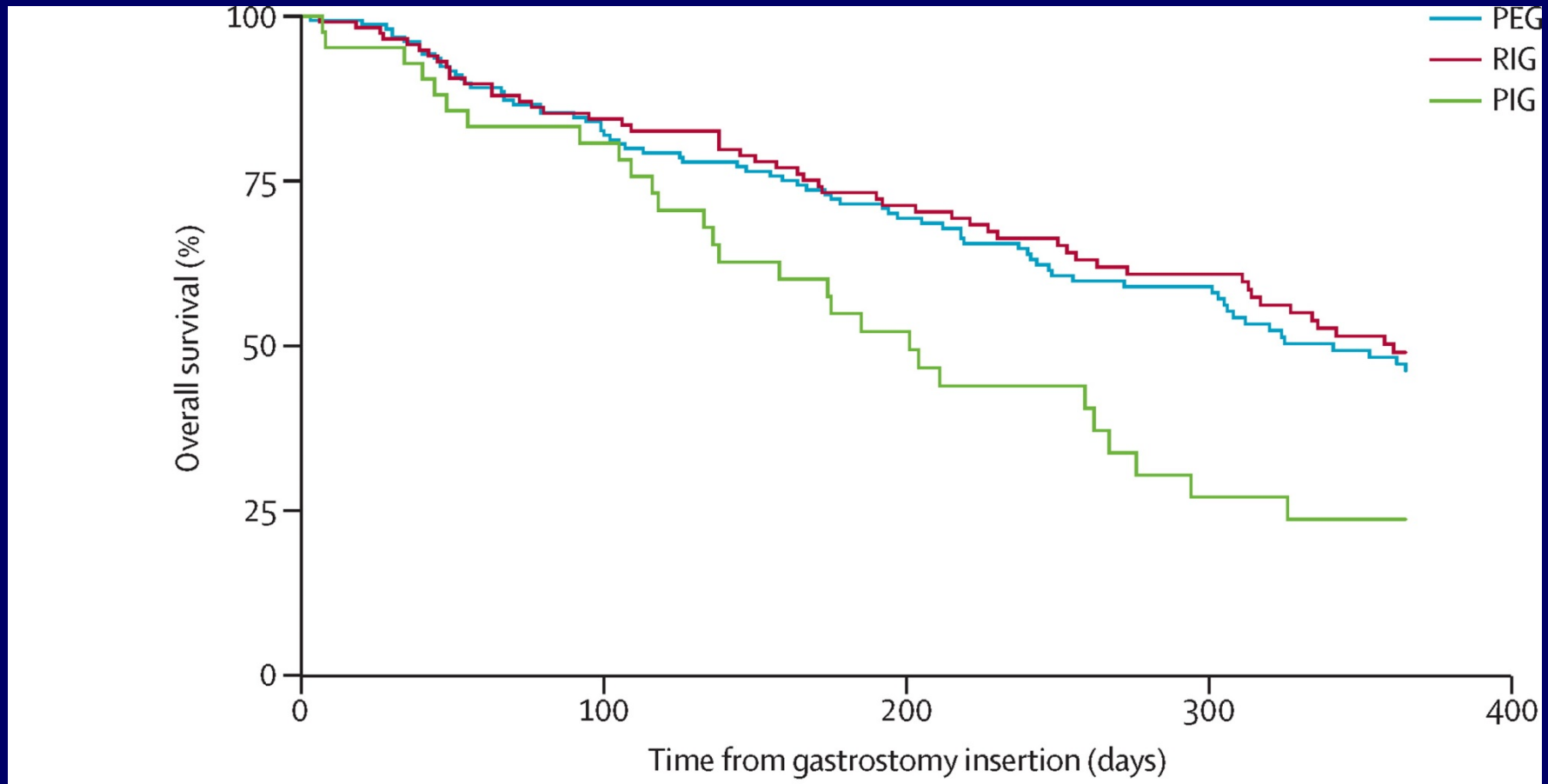
- Technique and survival
- Looked at PEG, RIG and PIG

- Percutaneous endoscopic…
- Radiologically inserted…
- Per-oral image-guided…..

PROGAS

- Median survival 325 days
- 4% 30 day mortality (prev. quoted 10% for all cause gastrostomy)
- No statistically significant difference between techniques

Survival by Technique



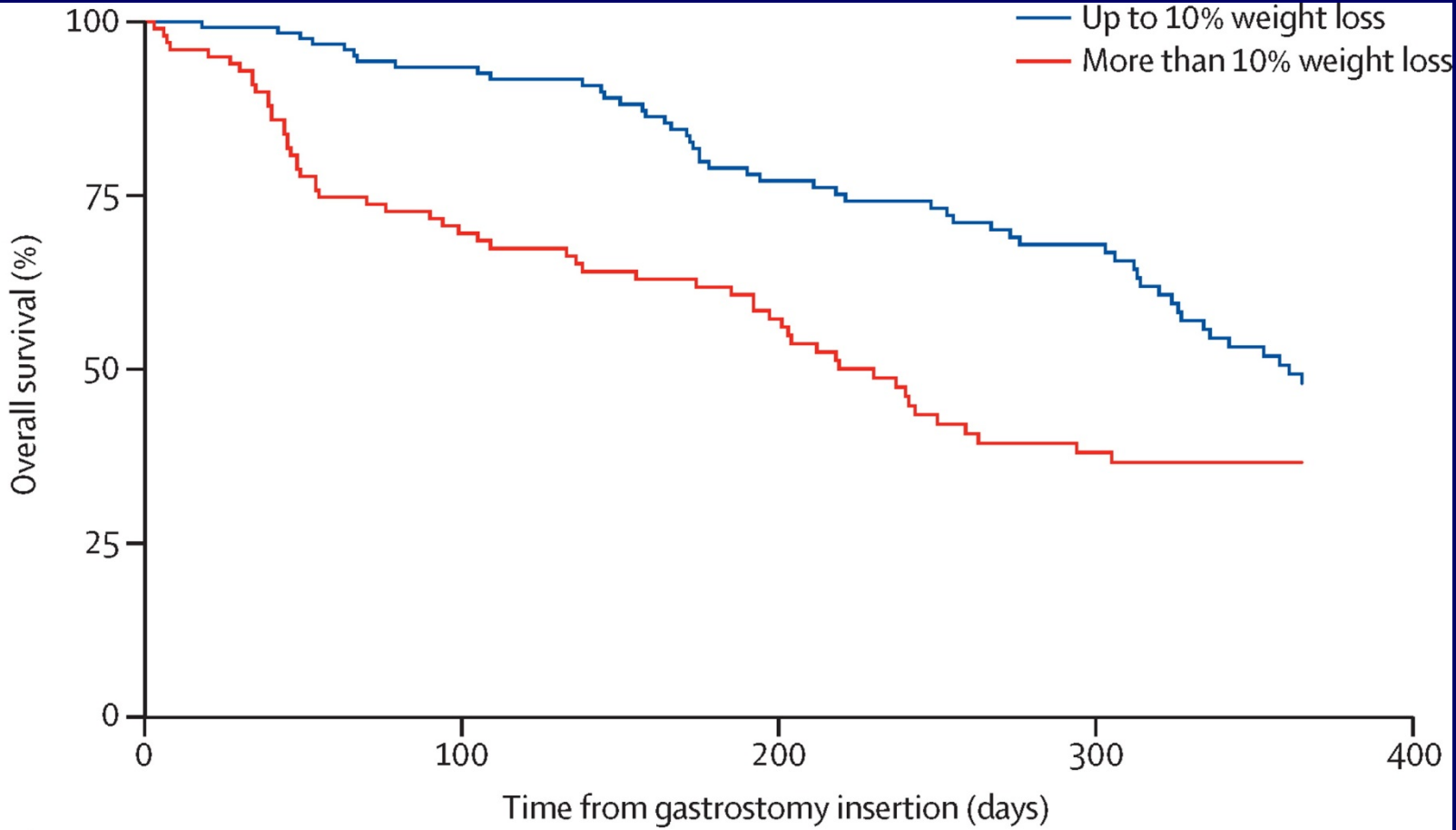
Number at risk

PEG	159	122	92	64
RIG	117	94	74	53
PIG	42	32	19	8

PROGAS

- Pre-procedural weight loss of >10% body mass at diagnosis assoc >X10 increase in 30 day mortality!

Survival by Weight Loss



Number at risk				
Up to 10% weight loss	124	107	82	58
More than 10% weight loss	99	66	48	28

PROGAS – Conclusions:

- Technique – PEG, RIG, PIG did not affect outcome/survival
- Pre-procedural wt loss key to survival, 10% loss the key figure
- No benefit in terms of weight gain, but continued loss poor prognostic indicator
- No significant effect on QoL, but caregiver strain higher!
- 30 day mortality 4%
- PostGAS

Conclusions

MND remains:

- a rapidly progressive neurodegenerative disease without effective modifying treatments with a poor prognosis
- a palliative based approach is appropriate
- All interventions, in the face of such a destructive condition, should be considered with a cautionary holistic approach.
- A robust evidence base is necessary to support interventional treatments

The Future:

- “Gene silencing” therapies emerging – but at present will not help more than 90% of MND patients!
- Better studies of the impact of gastrostomy (Post GAS) and nutritional interventions (HighCALS) coming !
- Complex complex but more inclusive treatment trials should speed up the “theory to therapy” treatment pipeline (MND-SMART, TRI-CALS)