

THE LANCET

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Supplementary appendix

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3. Bedford Hospital NHS Trust, Bedford: Sebastian **Clark**, Peter **Knowlden**, Malgorzata **Lowicka**, Maciej **Ryszka***
4. Chelsea and Westminster Hospital NHS Trust, London: Alina **Hua**, Vinothan **Loganathan***, Katarzyna **Mrozek**, Kylie **Norrie**, Marcela Paola **Vizcaychipi**
5. Churchill Hospital, Oxford University Hospitals NHS Trust, Oxford: Jagannath **Haldar***, Vipul **Jain**, Andris **Klucniks**
6. City Hospitals Sunderland NHS Trust, Sunderland: Ashley **Allan**, Sean **Cope**, Julie **Furneval**, Kiran Kumar **Koneti***, Ryszard **Palugniok**
7. Colchester Hospital University NHS Foundation Trust, Colchester: Elaine **Chinery**, Marianne **Morgan**, Lajos **Zsisku***
8. Darlington Memorial Hospital, Darlington: Amanda **Cowton**, James **Limb***, Amir **Rafi**, Radhika **Ramasamy**
9. Derriford Hospital Plymouth NHS Trust, Plymouth: Patrick **Abigail**, Stuart **Gallacher**, Benjamin **Hyams**, Gary **Minto***
10. Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust, Doncaster: Mary **Avvai***, Tejal **Desai**, Vinayak **Kumar**, Helen **Thornley**
11. Dorset County Hospital NHS Foundation Trust, Dorchester: Fiona **Linton**, Sarah **Moreton**, Mark **Pulletz***, Lydia **Richardson**
12. Glan Clwyd Hospital, Rhyl: Richard **Pugh**, Ramakrishnan **Shobha***, Stella **Wright**
13. Guys and St. Thomas' NHS Foundation Trust, London: Kira **Achaibar**, Heena **Bidd***, Nadia **Blunt**, Joanna **Booth**, Priyakam **Chondhury**, George **Christodoudiles**, John **Cronin**, Alexandra **Dumitrescu**, Ade **Hafisayena**, Maria **leong**, Sonja **Meier**, Zahra **Rajput**, Suneil **Ramessur**, Emma **Taylor**, Brian **Trethowan**

14. Harrogate District NHS Foundation Trust, Harrogate: Thomas **Collyer***, James **Featherstone**, Alice **Moull**
15. Hull and East Yorkshire NHS Trust, Hull: Caroline **Abernethy**, Packianathaswamy **Balaji***, Anna **Greenwood**, Kate **Henderson**, Ali **Husnain**, Ahmed **Hussein**, Victoria **Martinson**, David **Pickering**, Rajeskar **Ramachandran**, Neil **Smith**, Altaf **Sultanpori**
16. Isle of Wight NHS Trust, Newport: Gabor **Debreceeni***
17. Leicester hospitals NHS trust 1. Glenfield Hospital, Leicester: Dawn **Hales**, Sameer **Hanna-Jumma**, Gary **Lau***, Nathalie **Rich**
18. Leicester hospitals NHS trust 2. Leicester Royal Infirmary, Leicester: Sarah **Bowrey**, Vandana **Girotra**, Dawn **Hales**, Mary **Mushambi***, Andan **Patil**
19. Lewisham & Greenwich NHS Trust, London: Saif Nasr **Baluch**, James **Heaton**, Silvia **Leonardi**, Bernd Oliver **Rose***
20. Liverpool Women's NHS Foundation Trust, Liverpool: Emily **Christie***, Martin **Kelly**
21. Mid Cheshire Hospitals NHS Foundation Trust, Crewe: Vandana **Goel***, Daniel **Saul**, Ashok **Sinha**
22. Newcastle upon Tyne NHS Trust - 1. Freeman Hospital, Newcastle upon Tyne: Ahmad **Chishti***, Carmen **Scott**
23. Newcastle upon Tyne NHS Trust - 2. Royal Victoria Infirmary, Newcastle upon Tyne: David **Saunders**, Rhona **Sinclair***
24. Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich: Katie **Allan**, Tim **Baker**, Katrina **Barber**, Parveen **Dhillon**, Benjamin **Fox**, Siobhan **King**, Louise **Oduro-Dominah**, Caroline **Reavley***, Carmen **Soto**, Farooq **Brohi**, Prabhakar **Paranthaman**, Khalid **Siddiqi**
25. Northern Devon Healthcare NHS Trust, Barnstaple: Jane **Hunt**, Guy **Rousseau***, Amanda **Skinner**, Lucia **Stacombe**
26. Northern Lincolnshire and Goole NHS Trust, Scunthorpe: Sanjeev **Garg***
27. Poole Hospital NHS Foundation Trust, Poole: Helena **Barcraft-Barnes**, Julie **Camsooksai**, Carrie **Colvin**, Sarah **Jenkins**, Sarah **Patch**, Henrik **Reschreiter***, Lee **Tbaily**
28. Portsmouth NHS Trust, Portsmouth: Keith **Ritchie***, Jeremy **Nightingale**, Aneeta **Sinha**
29. Queen Victoria Hospital NHS Foundation Trust, East Grinstead: Julian **Giles***, Orla **Harvey**, Caroline **Nicholas**, Debbie **Weller**
30. Rotherham NHS Foundation Trust, Rotherham. Anil **Hormis***
31. Royal Devon and Exeter NHS Foundation Trust, Exeter: Leigh **Boxall**, Katherine **Curley**, Laurence **Helliwell**, Katie **Ilett**, Laurie **Kidd**, Maria **Nadolski**, Alison **Potter**, Richard **Telford***
32. Royal Hampshire County Hospital, Winchester: Jane **Martin**, Stephen **Townley***

33. Royal Liverpool University Hospital, Liverpool: James **Doolan**, Jennifer **Hunter**, Sam **Michlig**, Burra V.S. **Murthy***, Andrew **Rushton**, Deborah **Scanlon**
34. Royal Surrey County Hospital, Guildford: Smita **Gosavi**, Mehrun **Zuleika***
35. Royal Victoria Hospital Belfast, Belfast: Earlene **Armstrong**, Jonathan **Holland**, Killian **McCourt**, Claire **Montgomery**, Rosalind **O'Reilly**, James **Reid**, Martin **Shields***
36. Salisbury NHS Foundation Trust, Salisbury: Ilana **Delroy-Buelles**, James **Gaynor**, Christian **Schopflin***, Davina **Watson**
37. Scarborough Hospital, Scarborough: Ben **Chandler***, Daniel **Harper**
38. Northern General Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield: Helen **Ellis**, Sumayer **Sanghera***
39. South Tyneside District Hospital, South Shields: Christian **Frey***
40. Southampton University Hospital NHS Foundation Trust, Southampton: Emily **Adam**, Pauline **Bartlett**, Nigel **Beauchamp**, Thomas **Blincoe**, Robert **Charnock**, Nicola **Cox**, Mark **Edwards**, Lesley **Hawkins**, Samantha **Leggett**, Neil **McGill***, Robin **Wilson**
41. Southern Health & Social Care Trust, Portadown: Raymond **McKee***
42. St Helens and Knowsley Teaching Hospitals NHS Trust, Whiston: Karim **Mukhtar***
43. Leeds Teaching Hospitals NHS Trust, Leeds, Luke **Bishop**, Pawan **Gupta**, Carl **Ilyas**, Andrew **Lumb***, Olga **Plotnikova**, Roshan **Rao**, Rajendra **Singh**, Hao Ern **Tan**
44. St Richards Hospital, Chichester: Isobel **Amey**, Yolanda **Baird**, Anna **Carter**, Judith **Highgate**, Jordi **Margalef**, Michael **Margarson***, Sally **Moore**, Heather **Murray**, Tom **Standley**
45. The Dudley Group NHS Foundation Trust, Dudley: Clare **Allcock**, Kirsty **Baron**, Susan **Merotra**, Nahla **Farid ***, Julian **Sonksen**
46. The Ipswich Hospital NHS Trust, Ipswich: Stephanie **Bell**, Heather **Blaylock**, Vlad **Kushakovsky***
47. The James Cook University Hospital - South Tees NHS Foundation Trust, Middlesbrough: Emanuel **Cirstea**, Uwe **Franke***, Louise **Swan**
48. The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust, Oswestry: Kirsty **Davies**, Jayne **Edwards**, John **John***, Julie **Steen**
49. The Royal Bournemouth & Christchurch Hospitals NHS Foundation Trust, Bournemouth: James **Craig***, Emma **Willett**, Laura **Wood**
50. The Royal Derby Hospital, Derby: Tracy **Brear**, Charlotte **Downes**, Ryan **Humphries**, Susan **Melbourne**, David **Rogerson***, Stephen **Sarno**
51. The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham: Faye **Moore**, Sudeshkumar **Muniyappa**, Narendra **Siddaiah***
52. Torbay and South Devon NHS Foundation Trust, Torquay: Gill **Barnett**, Tom **Bradley**, Gabrielle **de Selincourt**, Aiden **Melia**, Pauline **Mercer**, Jane **Montgomery***

53. United Lincolnshire Hospitals NHS Trust, Lincoln: Nahla **Awad***, Jatin **Dedhia**, Suganthi **Joachim**, Usman **Razaque**
54. University Hospital of North Staffordshire NHS Trust, Stoke-on-Trent: Conrad **Hayes**, Samuel **Passey**, Nalwaya **Pramod***, Tamiselvan **Rajamanickam**, Siby **Sebastian**, Permendra **Singh**, Rajinikanth **Sundara Rajan**, Benedict **Williams**
55. University Hospital of North Durham, Durham: Louise **Duncan**, Melanie **Kent**, Selena **Sehgal**, Sameer **Somanath***
56. West Middlesex University Hospital NHS Trust, London: Matthew **Clayton**, Dominika **Dabrowska***, Maria **Georghiou**
57. West Suffolk Hospital NHS Foundation Trust, Bury St. Edmunds: Sally **Humphreys**, Christiane **Kubitzek***
58. Western General Hospital, Edinburgh: Colin **Baird***, Keith **Hodgson**, Foo **Irwin**, Susan **Midgley**, Elizabeth **Steel**, Ong **Suying**
59. York Teaching Hospitals NHS Foundation Trust, York: Simon **Davies***, Andy **Gibson**, Thomas **Smith**

Supplementary Material (Methods)

Recruitment rate	Inclusion
1/12 (= 8.3%)	All patients born in <u>one</u> randomly selected month
2/12 (= 16.6%)	All patients born in <u>two</u> randomly selected months
3/12 (= 25.0%)	All patients born in <u>three</u> randomly selected months
...	...
11/12 (= 91.7%)	All patients born in <u>eleven</u> randomly selected months
12/12 (= 100%)	All patients

Centres that had an estimated inclusion of at least 50 patients per week had the possibility to reduce their inclusion rate by a randomized selection process. Given the assumption that birth rates are the same in all months of the year, inclusion of patients was guided by their months of birth. For example, if a centre wished only to include 25% of its eligible patients, the ESA research team randomly chose three months of the year. Accordingly, this specific centre only included patients born in these allocated months. The table depicts examples of recruitment rates and the resulting number of birth months.

Table S1: Randomised Selection Process

Neuromuscular blocking agent	Dose [mg]*	Body weight [kg]*	Dose [mg/kg]	2 x ED ₉₅ [mg/kg]**	Duration of 2 x ED ₉₅ to TOFR ≥ 0.9 [min]**	Estimated duration of each given dose [min]
Succinylcholine	70	70	1.00	0.7	8	11
Atracurium			0.00	0.5	35	0
Cisatracurium	8	70	0.11	0.1	45	51
Mivacurium	5	70	0.07	0.2	20	10
Rocuronium			0.00	0.6	40	0
Vecuronium			0.00	0.1	45	0
Pipecuronium			0.00	0.1	75	0
Pancuronium			0.00	0.1	75	0
Estimated duration to TOFR ≥ 0.9 of all given doses (sum of the column)						72

Twice the ED₉₅ of a neuromuscular blocking agent has a recognised duration of action to recovery of the train-of-four ratio ≥ 0.9. A prolongation of the duration by 20% was considered if anaesthesia was maintained using an inhalational agent for more than 45min according to Motamed et al.¹ and Withington et al.². To demonstrate the calculation matrix an example of a patient is given: 70 kg (body weight) receiving succinylcholine 70 mg, followed by cisatracurium 8 mg and mivacurium 5 mg.

TOFR = train-of-four ratio

* Data are to be copied from the CRF

** 2 x ED₉₅ for the various neuromuscular blocking agents and their duration to TOFR ≥ 0.9 according to Fink et al.³ or Lee et al (succinylcholine)⁴

Estimated duration of each given dose is calculated by: Dose / 2 x ED₉₅ x (Duration of 2 x ED₉₅ to TOFR ≥ 0.9)

Table S2. Calculation Sheet for the Dosing Technique of Neuromuscular Blocking Agents

¹ Motamed C, Donati F. Sevoflurane and isoflurane, but not propofol, decrease mivacurium requirements over time. *Can J Anaesth* 2002;49:907-12.

² Withington DE, Donati F, Bevan DR, Varin F. Potentiation of atracurium neuromuscular blockade by enflurane: time-course of effect. *Anesth Analg* 1991;72:469-73.

³ Fink H, Blobner M, Martyn JAJ. Neuromuscular blocking drugs. In: Evers AS, Maze M, Kharasch ED, eds. *Anesthetic pharmacology*. 2 ed. New York, NY, USA: Cambridge University Press; 2011:608-32.

⁴ Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, Naguib M. Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: a comparison with spontaneous recovery from succinylcholine. *Anesthesiology* 2009;110:1020-5

Supplementary Material (Results)

Factor	OR _{adj.} (95%-CI)	p-value
NMBA used	1.86 (1.53–2.26)	< 0.0001
Age > 60 yrs	1.69 (1.48–1.94)	< 0.0001
Male sex	1.06 (0.95–1.19)	0.30
BMI < 17, BMI > 30 kg/m ² , BMI not available	1.41 (1.25–1.60)	< 0.0001
ASA status ≥ III	2.06 (1.81–2.35)	< 0.0001
Heart failure ≥ NYHA II	1.37 (1.15–1.64)	0.0004
Coronary artery disease	1.00 (0.85–1.17)	0.99
Neurologic disease	1.10 (0.94–1.29)	0.22
Diabetes mellitus	1.04 (0.90–1.20)	0.62
Liver disease	1.25 (1.01–1.54)	0.042
Creatinine clearance < 90 ml/min	1.26 (1.11–1.44)	0.0003
Chronic obstructive pulmonary disease	1.43 (1.21–1.69)	< 0.0001
Asthma	1.32 (1.08–1.61)	0.0067
Obstructive sleep apnoea syndrome	1.04 (0.81–1.34)	0.76
Recent respiratory infection	1.88 (1.49–2.38)	< 0.0001
Smoker	1.33 (1.15–1.53)	< 0.0001
Preoperative SpO ₂ ≤ 94%	2.35 (2.05–2.70)	< 0.0001
Emergency surgery	2.24 (1.96–2.56)	< 0.0001
Intrathoracic or open upper abdominal surgery	3.53 (3.09–4.03)	< 0.0001
Duration of surgery > 2h	2.34 (2.09–2.63)	< 0.0001
Total intravenous anaesthesia	_*	_*
Endotracheal intubation	_**	_**

NMBA= Neuromuscular blocking agent, BMI = Body Mass Index, NYHA = New York Heart Association, SpO₂ = peripheral oxygen saturation, OR_{adj.} = adjusted odds ratio, CI = confidence interval, POPC = postoperative pulmonary complication

* Not included co-factors due to univariate analysis $p \geq 0.005$

** Not included due to correlation with "NMBA used" ($r^2 > 0.5$).

The odds ratio for NMBA was additionally adjusted for European region, recruitment rate of participating hospitals, and use of pulseoximetry for postoperative POPC screening.

Table S3: Multivariate Analysis in All Anaesthetized Patients (Sub-cohort 1)

Key factor / Models	OR _{adj.} (95% CI)
Use of any Neuromuscular Blocking Agent (NMBA) in Sub-Cohort 1 (n=21,694)	
Multivariate logistic regression (Analysis per protocol)	1.86 (1.53–2.26)
Multivariate logistic regression (including ARISCAT categories)	1.84 (1.52–2.23)
Proportional hazard model, HR _{adj.} *	1.81 (1.51–2.18)
Multivariate logistic regression (without dichotomization)**	1.55 (1.25–1.91)
Weighted meta-analysis of OR of terminal nodes created by CART (n=21,464).	1.72 (1.42–2.10)
Weighted meta-analysis of OR of deciles of increasing propensity to use NMBAs.	1.57 (1.20–2.00)
Propensity score matching (1:1 match, caliper=0.0001 resulting in n=4,550)	1.82 (1.27–2.61)
Multivariate logistic regression "use of NMBA for intubation only" (n=13,044).	1.51 (1.20–1.90)
Multivariate logistic regression using intermediate or severe POPC as outcomes	1.63 (1.28–2.09)
Multivariate logistic regression using early POPC as outcomes	2.28 (1.78–2.92)
Use of High Doses (with an Expected Duration ≥ 159min) of NMBA in Sub-Cohort 2 (n=17,150)	
Multivariate logistic regression (Analysis per protocol)	1.03 (0.88–1.20)
Proportional hazard model (p=0.2), HR _{adj.} *,***	1.07 (0.86–1.35)
Multivariate logistic regression (p=0.9, without dichotomization)** ,***	0.91 (0.70–1.19)
Weighted meta-analysis of OR of terminal nodes created by CART.	1.16 (0.98–1.37)
Weighted meta-analysis of OR of deciles of increasing propensity to use high doses of NMBA.	1.04 (0.90–1.21)
Propensity score matching (1:1 match, caliper=0.0001 resulting in n=1,958)	1.01 (0.75–1.36)
Multivariate logistic regression using intermediate or severe POPC as outcomes	1.11 (0.92–1.34)
Use of any Neuromuscular Muscular Monitoring (NMM) in Sub-Cohort 2 (n=17,150)	
Multivariate logistic regression (Analysis per protocol)	1.31 (1.15–1.49)
Proportional hazard model, HR _{adj.} *	1.24 (1.11–1.38)
Multivariate logistic regression (without dichotomization)**	1.32 (1.16–1.50)
Weighted meta-analysis of OR of terminal nodes created by CART.	1.58 (1.39–1.79)
Weighted meta-analysis of OR of deciles of increasing propensity to use NMM.	1.24 (1.11–1.40)
Propensity score matching (1:1 match, caliper=0.0001 resulting in n=5,076)	1.32 (1.07–1.63)
Multivariate logistic regression using intermediate or severe POPC as outcomes	1.13 (0.97–1.33)
Use of any Reversal Agent in Sub-Cohort 2 (n=17,150)	
Multivariate logistic regression (Analysis per protocol)	1.23 (1.07–1.41)
Proportional hazard model, HR _{adj.} *	1.19 (1.06–1.34)
Multivariate logistic regression (without dichotomization)**	1.25 (1.09–1.44)
Weighted meta-analysis of OR of terminal nodes created by CART.	1.25 (1.11–1.41)
Weighted meta-analysis of OR of deciles of increasing propensity to use reversal agents.	1.19 (1.05–1.36)

Propensity score matching (1:1 match, caliper=0.0001 resulting in n=4,386)	1.25 (1.00–1.56)
Multivariate logistic regression using intermediate or severe POPC as outcomes	1.36 (1.14–1.61)
Use of any Quantitative vs. Qualitative NMM in Sub-Cohort 3 (n=6,868)	
Multivariate logistic regression (Analysis per protocol)	1.07 (0.90–1.29)
Proportional hazard model, HR _{adj.} *	1.08 (0.89–1.29)
Multivariate logistic regression (without dichotomization)**	1.06 (0.91–1.24)
Weighted meta-analysis of OR of terminal nodes created by CART.	0.94 (0.78–1.12)
Weighted meta-analysis of OR of deciles of increasing propensity to use quantitative NMM.	1.03 (0.87–1.22)
Propensity score matching (1:1 match, caliper=0.0001 resulting in n=1,294)	1.02 (0.69–1.51)
Multivariate logistic regression using intermediate or severe POPC as outcomes	0.94 (0.75–1.17)
Extubation at Train-of-four Ratio (TOFR) ≥ 0.9 in Sub-Cohort 4 (n=4,182)	
Multivariate logistic regression (Analysis per protocol)	1.03 (0.82–1.31)
Proportional hazard model, HR _{adj.} *	1.03 (0.86–1.27)
Multivariate logistic regression (without dichotomization)**	1.03 (0.81–1.31)
Weighted meta-analysis of OR of terminal nodes created by CART.	1.07 (0.86–1.33)
Weighted meta-analysis of OR of deciles of increasing propensity to extubate at train-of-four ratio (TOFR) ≥ 0.9.	1.07 (0.86–1.33)
Propensity score matching (1:1 match, caliper=0.0001, resulting in n=498)	0.80 (0.44–1.44)
Multivariate logistic regression using intermediate or severe POPC as outcomes	1.21 (0.90–1.63)
Use of Sugammadex vs. Neostigmine in Sub-Cohort 5 (n=8,795)	
Multivariate logistic regression (Analysis per protocol)	1.03 (0.85–1.25)
Proportional hazard model, HR _{adj.} *	1.01 (0.86–1.19)
Multivariate logistic regression (without dichotomization)**	1.06 (0.89–1.30)
Weighted meta-analysis of OR of terminal nodes created by CART.	1.16 (0.97–1.38)
Weighted meta-analysis of OR of deciles of increasing propensity to use Sugammadex.	1.03 (0.87–1.23)
Propensity score matching (1:1 match, caliper=0.0001 resulting in n=1,380)	0.93 (0.63–1.36)
Multivariate logistic regression using intermediate or severe POPC as outcomes	0.93 (0.74–1.18)
CART = classification and regression tree, OR _{adj.} = adjusted odds ratio, POPC = postoperative pulmonary complication	
* the proportional hazard model (Cox-model) includes the time between anaesthesia and the day of the diagnosis of POPC, the risk of POPC is given as adjusted hazard ratio (HR _{adj.}), see also figure S2	
** the top 10 factors with the highest effect size are included without dichotomization	
*** the key factor is also included without dichotomization, p-value is given for the overall comparison, OR _{adj.} is given for the comparison between 1 st and 5 th quintile	

Table S4: Sensitivity Analyses Using Several Statistical Models.

Co-factor	p-value of interaction term “Use of NMBA” x co-factor
Age	0.93
Body mass index	0.87
ASA classification	0.41
Preoperative SpO ₂	0.93
Type of surgery	0.98
Duration of surgery	0.67

The interaction terms between “Use of neuromuscular blocking agents” and the major influencing co-factors are added to the logistic regression model and tested for significant modification of the key factor “Use of neuromuscular blocking agents”. None of these co-factors proved to modify the key factor. Therefore, interaction terms are excluded from the analyses per protocol. ASA = American Society of Anesthesiology. NMBA = neuromuscular blocking agent

Table S5: P-values of Interaction Terms in Sub-cohort 1 (Anaesthetised Patients)

Factor	OR _{adj.} (95%-CI)	p-value
More than one NMBA given	0.86 (0.71–1.04)	0.12
Expected duration of NMBA ≥ 159 min	1.03 (0.88–1.20)	0.75
Any incremental dose given	1.27 (1.10–1.48)	0.0017
NMM applied	1.31 (1.15–1.49)	< 0.0001
Reversal agent given	1.23 (1.07–1.41)	0.0028
Age>60 yrs	1.65 (1.43–1.92)	< 0.0001
Male sex	1.04 (0.92–1.18)	0.52
BMI<17, BMI > 30 kg/m ² , BMI not available	1.42 (1.24–1.62)	< 0.0001
ASA status ≥ III	1.94 (1.69–2.24)	< 0.0001
Heart failure ≥ NYHA II	1.42 (1.17–1.72)	0.0003
Coronary artery disease	1.01 (0.85–1.20)	0.93
Neurologic disease	1.11 (0.93–1.32)	0.25
Diabetes mellitus	1.08 (0.92–1.27)	0.36
Liver disease	1.32 (1.05–1.64)	0.015
Creatinine clearance < 90 ml/min	1.29 (1.12–1.48)	0.0004
Chronic obstructive pulmonary disease	1.36 (1.13–1.64)	0.0011
Asthma	1.36 (1.09–1.69)	0.0062
Obstructive sleep apnoea syndrome	1.01 (0.77–1.34)	0.92
Recent respiratory infection	1.84 (1.43–2.37)	< 0.0001
Smoker	1.41 (1.21–1.64)	< 0.0001
Preoperative SpO ₂ ≤ 94%	2.36 (2.03–2.74)	< 0.0001
Emergency surgery	2.30 (1.97–2.68)	< 0.0001
Thoracic or open upper abdominal surgery	3.01 (2.60–3.48)	< 0.0001
Duration of surgery > 2h	1.65 (1.41–1.93)	< 0.0001
Total intravenous anaesthesia	_*	_*
Endotracheal intubation	1.36 (0.87–2.11)	0.18
Long and intermediate acting NMBAs	1.25 (0.87–1.81)	0.23
Extubation at intensive care unit	1.37 (1.03–1.83)	0.032
NMM added to decide extubation readiness	_**	_**
Time from first NMBA to extubation > 4h	1.77 (1.49–2.11)	< 0.0001

NMBA = neuromuscular blocking agent, NMM = neuromuscular monitoring, NYHA = New York Heart Association, SpO₂ = peripheral oxygen saturation, OR_{adj.} = adjusted odds ratio, CI = confidence interval, POPC = postoperative pulmonary complication

* Not included co-factors due to univariate analysis $p \geq 0.005$

** Not included due to correlation with "NMM" ($r^2 > 0.5$)

The odds ratios are additionally adjusted for European region, recruitment rate of participating hospitals, and use of pulseoximetry for postoperative POPC screening.

Table S6: Multivariate Analysis in Patients Receiving Neuromuscular Blocking Agents (Sub-cohort 2)

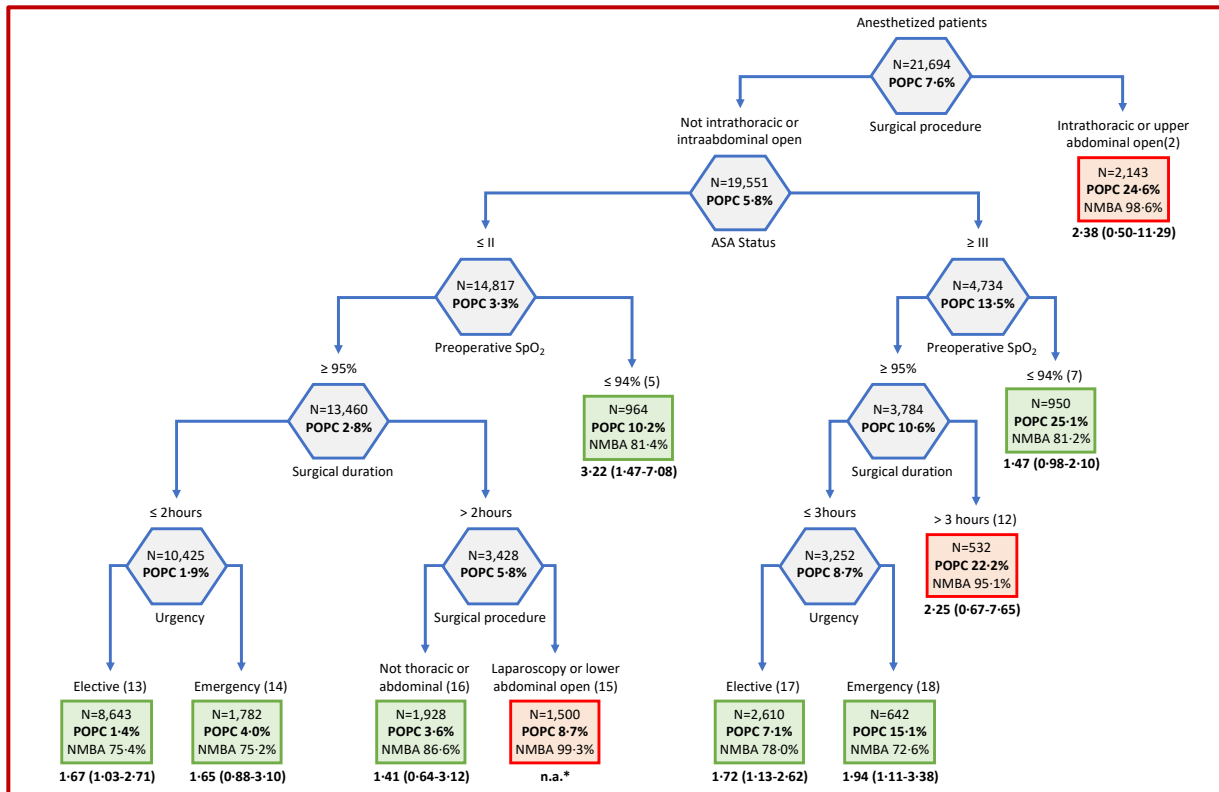


Figure S1: Classification Tree Analysis in Anaesthetized Patients.

Hexagons are interior nodes, rectangles are terminal nodes. Each node represents a set of patients. Interior nodes are split into two subsets of patients with the best homogeneity of postoperative pulmonary complications (POPC). Green rectangles are terminal nodes representing 80.8% of anaesthetized patients with a mean likelihood of 77.5% to receive neuromuscular blocking agents (NMBA) and a 5.0% risk of POPC. Terminal nodes are depicted in red if the likelihood of NMBA use is > 95% (mean 98.4%) representing 19.2% of anaesthetized patients: all cases of intrathoracic surgery and upper abdominal open surgery, cases of any other surgery lasting ≥ 3 hours in ASA III-V patients with preoperative SpO₂ $\geq 95\%$, and cases of laparoscopic or lower abdominal open surgery lasting ≥ 2 hours (ASA I-II and SpO₂ $\geq 95\%$). These patients have a high risk of POPC (18.6%).

In each terminal node a univariate analysis of the effect of use of a NMBA on POPC is performed. The odds ratio (95% confidence interval) is given under each terminal node. These odds ratios are combined using random effects meta-analysis (OR: 1.75 (1.44–2.13), $z=5.68$, $p<0.0001$; heterogeneity: $I^2=0\%$, $\tau^2=0$, $p=0.87$). Patients with a high likelihood to receive a NMBA and a high risk of POPC (red rectangles) do not make as great a contribution to the effect of NMBA on POPC (combined weight 5.6%) due to the low rate of patients not receiving NMBAs (1.6%). Conclusions about the increased risk of using NMBAs should therefore exclude the latter groups of patients (red rectangles).

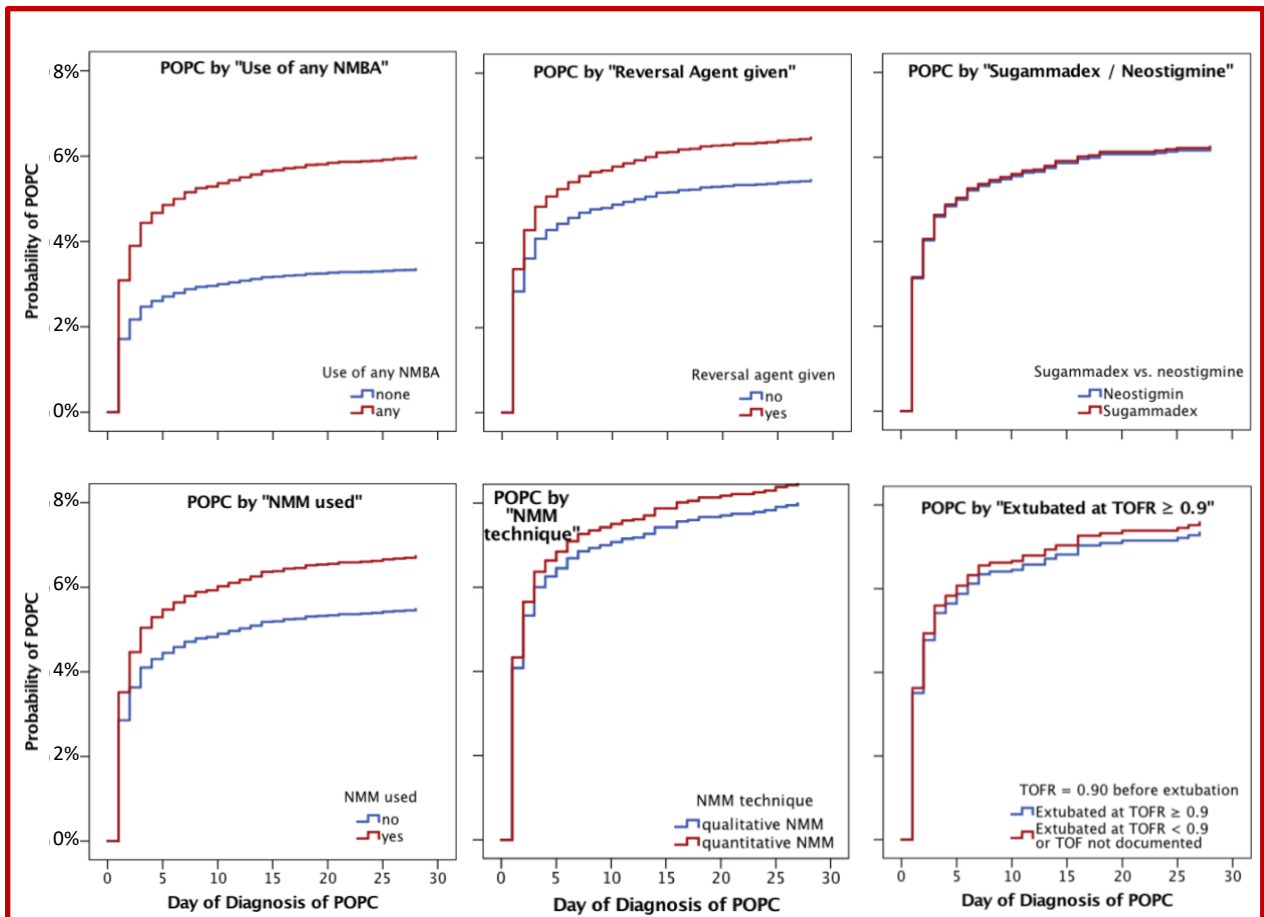



Figure S2: Cox-Proportional Hazards Model for Postoperative Pulmonary Complications during Hospital Stay.

The adjusted hazard ratios of the six models are given in table S5. The probabilities are calculated using means of the co-factors of each model. POPC=postoperative pulmonary complication.

NMBA=neuromuscular blocking agent. NMM=neuromuscular monitoring. TOFR=train-of-four ratio.

Printout of the electronic Case Report Form

	PO stanaesthesia PUL monary complications A fter use of muscle R elaxants in Europe (POPULAR) Observational Study Screening - Exclusion Form
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Subject exclusion criteria: (Yes=exclusion from study)

1.	Is Patient less than 18 years of age?	<input type="checkbox"/> No	<input type="checkbox"/> Yes
2.	Is Patient Scheduled for local or regional anaesthesia only ?	<input type="checkbox"/> No	<input type="checkbox"/> Yes
3.	Is patient's Anaesthetic procedure scheduled outside an operating room ?	<input type="checkbox"/> No	<input type="checkbox"/> Yes
4.	Is this an ambulatory Patient or a patient planned to be discharged within 12 hours postanaesthesia ?	<input type="checkbox"/> No	<input type="checkbox"/> Yes
5.	Is Patient's trachea intubated preoperatively ?	<input type="checkbox"/> No	<input type="checkbox"/> Yes
6.	Is Patient from an intensive care unit (ICU) ?	<input type="checkbox"/> No	<input type="checkbox"/> Yes
7.	Is Patient scheduled for additional Surgical / Anaesthetic procedure in the next 7 days ?	<input type="checkbox"/> No	<input type="checkbox"/> Yes
8.	Did Patient have a Surgical / Anaesthetic procedure within the past 7 days ?	<input type="checkbox"/> No	<input type="checkbox"/> Yes

If patient has "YES" to any of the exclusion criteria only this form should be completed and patient should not be entered in the CRF/electronic CRF



POstanaesthesia **PUL**monary complications **A**fter use of muscle **R**elaxants in Europe
(POPULAR) Data acquisition sheets - Case Report Form

CRF01 – Pre and Intra-operative Data

I. Informed Consent:

1. **Consent applicable?** No Yes (*choose No if waived by local EC*)
- 1.1 **If yes, was consent obtained?** No Yes
- 1.1.1 **If yes, date of informed consent:** - - ||| (dd-Mmm-YYYY) [\geq 01-Jul-2014]
2. **Study Subject ID:** - - ||| Enter Study Subject ID in this format xxx-xxx-xxx using a 3 digit code for the country, 3 digit code for the hospital and 3 digit individual patient number, separated with hyphens. It must be the same number as entered before.

II. Physical characteristics:

3. **Age:** years [18-120] 5. **Height** [100-230] cm
4. **Gender:** Male Female 6. **Weight** [30.0-400.0] . kg
7. **ASA Physical Status:** (*Choose single most appropriate*) I II III IV V

III. Medical History:

8. **History of heart failure:** (*Declared by the patient or recorded in chart*)
 = No = NYHA 1 = NYHA 2 = NYHA 3 = NYHA 4
9. **Coronary artery disease:** (*Declared by the patient or recorded in chart*) No Yes
10. **Neurologic disease:** (*Declared by the patient or recorded in chart*) No Yes
11. **History of Diabetes Mellitus:** No Yes
Answer „yes“ or „no“ to the question: „Has any physician told you that you have diabetes or are you on a diet to control your blood sugar values or do you take medication to control you blood sugar levels?“
12. **Liver disease** (*Declared by the patient or recorded in chart*) No Yes
13. **Preoperative serum creatinine available?** No Yes
- 13.1. **If yes, specify latest value before surgery:** . μ mol/L [1.0-3000.0]
- 13.2. **Indicate units:** mg/dL [0.1-30.0]

IV. Preoperative Respiratory Status:

14. **History of Chronic Obstructive Pulmonary Disease (COPD)?** No Yes
Answer „yes“ or „no“ to the question: „Has any physician told you that you have a chronic respiratory disease, such as chronic bronchitis or emphysema?“
15. **Is there any history of asthma?** No Yes
16. **Is there any history of sleep apnea?** No Yes
17. **Is there any history of recent respiratory infection (within the last 2 weeks)?** No Yes
18. **Patient smokes at least 1 cigarette/day for at least 3 months before the operation?** No Yes
19. **Preoperative SpO₂ (oxyhaemoglobin saturation by pulse oximetry):** % [50-100]
SpO₂ recorded in supine position after 1 minute breathing room air

V. Surgical Details:

20. Urgency of surgery:

non emergency emergency

21. Surgical procedure: (Choose single most appropriate)

- Intrathoracic open (e.g. thoracotomy or sternotomy)
 Intrathoracic closed (e.g. thoracoscopy or mediastinoscopy)
 Upper abdominal open (e.g. subcostal or supraumbilical laparotomy)
 Upper abdominal closed (e.g. laparoscopic or endoscopic)

- Lower abdominal closed
 Lower abdominal open
 Head and neck
 Craniotomy
 Peripheral or other procedures (e.g. orthopaedic, peripheral vascular, plastic surgery, arthroscopy, endoscopic urologic procedures as TURBK)

Surgical incision:

22. Incision Time |__|__|:|__|__| [0-23hrs] [0-59min] 23. Incision Date |__|__| - |__|__|__| - |__|__|__| [>=01-Jul-2014]

End of surgery:

24. End Time |__|__|:|__|__| [0-23hrs] [0-59min] 25. End Date |__|__| - |__|__|__| - |__|__|__| [>=01-Jul-2014]

VI. Anaesthetic details during surgery:

26. Maintenance of anaesthesia based on:

Volatile Total intravenous anaesthesia

27. Endotracheal intubation:

No Yes

28. Did the patient receive any muscle relaxant?

No Yes

28.1. Time of first dose muscle relaxant: |__|__| : |__|__| HH:MM [0-23hrs] [0-59min]

28.2. Date of first dose muscle relaxant: |__|__| - |__|__|__| - |__|__|__| [>=01-Jul-2014]

If yes, please specify drug and TOTAL dose during anaesthesia:

28.3. Succinylcholine No Yes If yes, TOTAL dose |__|__|__| mg [1-500]

28.4. Atracurium No Yes If yes, TOTAL dose |__|__|__| mg [1-500]

28.5. Cisatracurium No Yes If yes, TOTAL dose |__|__|__| mg [1-500]

28.6. Mivacurium No Yes If yes, TOTAL dose |__|__|__| mg [1-500]

28.7. Rocuronium No Yes If yes, TOTAL dose |__|__|__| mg [1-500]

28.8. Vecuronium No Yes If yes, TOTAL dose |__|__|__| mg [1-100]

28.9. Pancuronium No Yes If yes, TOTAL dose |__|__|__| mg [1-100]

28.10. Other NMBA No Yes

28.11. If yes, name: _____ (Please enter generic name for drug, no brand name)
If yes, TOTAL dose |__|__|__| mg [0-500]

28.12. Specify what drug was the last dose of muscle relaxant given: (Choose single most appropriate)

Succinylcholine Atracurium Cisatracurium Mivacurium
 Rocuronium Vecuronium Pancuronium Other

28.12.1 If other NMBA, specify: _____

28.13. Dose of the last muscle relaxant: |__|__|__| mg [0-500]

28.14. Time of last dose muscle relaxant: |__|__| : |__|__| HH:MM [0-23hrs] [0-59min]

28.15. Date of last dose muscle relaxant: |__|__| - |__|__|__| - |__|__|__| [>=01-Jul-2014]

29. Neuromuscular monitoring during surgery: (Choose single most appropriate)

- None Tactile/visual with nerve stimulator Acceleromyography (e.g. TOF Guard, TOF Watch)
 Electromyography (e.g. GE EMG) Kinemyography (e.g. GE NMT module)

VII. Emergence from anaesthesia:

30. **Neuromuscular monitoring during emergence from anaesthesia:** (Choose single most appropriate)

- None Tactile/visual with nerve stimulator Acceleromyography (e.g. TOF Guard, TOF Watch)
 Electromyography (e.g. GE EMG) Kinemyography (e.g. GE NMT module)

31. **Reversal agent:** No Yes **If yes, please specify reversal agent:**

31.1. **Neostigmine** No Yes If yes, total dose |_|_| . |_|_| mg [0.0-9.9]

31.2. **Other Cholinesterase inhibitor** (pyridostigmine, edrophonium) No Yes If yes, TOTAL dose
|_|_|_| . |_|_| mg [0.0-25.0]

31.3. **Sugammadex** No Yes If yes, total dose |_|_|_|_| mg [0.0-2000]

31.4. **If yes, reason for administration :** (Choose single most appropriate)

- routine practice clinical signs of residual block residual block indicated from neuromuscular monitoring

31.5. **Administration time of last reversal agent:** |_|_|:|_|_| HH:MM [0-23hrs] [0-59min]

If more than one dose or drug was given, please document the date and time of the last drug dose!

31.6. **Date of administration of reversal agent:** |_|_| - |_|_|_| - |_|/|_|/|_|/ [≥=01-Jul-2014]

31.7. **Was neuromuscular function monitored before reversal?** No Yes

31.7.1. **If yes, time of measurement:** |_|_|:|_|_| HH:MM [0-23hrs] [0-59min]

31.7.2. **If yes, specify date of measurement:** |_|_| - |_|_|_| - |_|/|_|/|_|/ [≥=01-Jul-2014]

31.7.3. **Number of twitches (TOF count):** |_| [0-4]

31.7.4. **Train-of-four ratio (if measured):** |_|_|_| % [0-200]

32. **Extubation within 6 hours after end of surgery?** No Yes

32.1. **If yes, date extubation:** |_|_| - |_|_|_| - |_|/|_|/|_|/ [≥=01-Jul-2014]

32.2. **If yes, time extubation :** |_|_|:|_|_| HH:MM [0-23hrs] [0-59min]

32.3. **If yes, extubation location:** (Choose single most appropriate)

- operating room PACU/Recovery room intensive care unit

32.4. **If yes, extubation criteria:** (Choose single most appropriate)

- clinical criteria neuromuscular monitoring clinical criteria and neuromuscular monitoring

32.5. **Was neuromuscular function monitored before extubation?** No Yes

32.5.1. **If yes, date of measurement:** |_|_| - |_|_|_| - |_|/|_|/|_|/ [≥=01-Jul-2014]

32.5.2. **If yes, time of measurement:** |_|_|:|_|_| HH:MM [0-23hrs] [0-59min]

32.5.3. **If yes, number of twitches (TOF count):** |_| [0-4]

32.5.4. **If yes, train of four ratio (if measured):** |_|_|_| % [0-200]

VIII. Discharge from OR

33. **After discharge from OR, patient:** (Choose single most appropriate)

- is transferred to PACU/Recovery room goes to ICU / ward
 is discharged from hospital to home is transferred to ICU/PACU/ Recovery Room and remains intubated
 has died

33.1. **If patient has died, date of death:** |_|_| - |_|_|_| - |_|_|_|_| [≥=01-Jul-2014]

33.2. **Suspected cause of death:** Pulmonary Cardiac (e.g. myocardial infarction) Central nervous, Sepsis,
Other (non pulmonary)

- If patient goes to ICU / ward, or stays on ward please complete CRF04
- If patient is discharged from hospital to home or dies, please stop data entry

CRF04 – Follow-up Visit (Discharge or Day 28)

Please record complications between “Postanaesthesia Visit” (Day 1, 2 or 3) and day of discharge from hospital. If patient is still in hospital, please record complications between “Postanaesthesia Visit” (Day 1, 2 or 3) and Day 28.

I. Postoperative pulmonary complications (POPC): between “Postanaesthesia Visit” and Discharge or Day 28

1. **Respiratory failure:** No Mild Intermediate Severe (ALI/ARDS)

Mild: $PaO_2 < 60$ mmHg or 8kPa or $SpO_2 < 90$ % in room air but responding to mask / nasal supplemental oxygen (excluding hypoventilation)

Intermediate: need for non-invasive or invasive mechanical ventilation due to a $PaO_2 < 60$ mmHg or 8kPa or $SpO_2 < 90$ % (excluding hypoventilation)

Severe (ALI/ARDS): need for invasive mechanical ventilation and $PaO_2/FiO_2 < 300$ mmHg or 40kPa regardless of level of PEEP

1.1. **Date of diagnosis of respiratory failure:** - - / / / [\geq 01-Jul-2014]

2. **Suspected pulmonary infection:** No Yes

Answer „yes“ if patient receives antibiotics , temperature $> 38^\circ C$, OR leucocytosis $> 12,000/\mu l$ AND meets a least one of the following criteria: new or changed sputum, new or changed lung opacity on chest X-ray when clinically indicated

2.1. **First day of postoperative pulmonary infection:** - - / / / [\geq 01-Jul-2014]

3. **Suspected pulmonary infiltrates:** No Yes

Chest X-ray demonstrating monolateral or bilateral opacities

3.1. **First day suspected pulmonary infiltrate:** - - / / / [\geq 01-Jul-2014]

4. **Atelectasis:** No Yes

Suggested by lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area and compensatory overinflation of the adjacent nonatelectatic lung

4.1. **First day of atelectasis diagnosis :** - - / / / [\geq 01-Jul-2014]

5. **Aspiration pneumonitis:** No Yes

Defined as respiratory failure after the inhalation of regurgitated gastric contents

5.1. **First day of evidence of aspiration pneumonitis:** - - / / / [\geq 01-Jul-2014]

6. **Bronchospasm:** No Yes

Defined as newly detected expiratory wheezing treated with bronchodilators

6.1. **Date of bronchospasm:** - - / / / [\geq 01-Jul-2014]

7. **Pulmonary oedema:** No Yes

Defined as diffuse alveolar interstitial infiltrates with dyspnea and rales related to left ventricular failure, confirmed by one of the following: echocardiography, pulmonary catheter or clinical improvement with specific treatment

7.1. **Date pulmonary oedema:** - - / / / [\geq 01-Jul-2014]

8. **Did the patient have an unexpected additional surgical/anaesthetic procedure after the first operation (inclusion) and day 28 ?** No Yes 8.1 If yes, give date of first re-operation : - - / / /

8.2 If yes, number of re-operations: [1-20] [\geq 01-Jul-2014]

9. **Date of Discharge (or death or date of day 28 if patient is still in hospital)?** - - / - - /

10. **If dead, suspected cause of death:** Pulmonary [\geq 01-Jul-2014]

Cardiac (e.g. myocardial infarction) Central nervous, Sepsis, Other (non pulmonary)