

# Anaesthesia

## Association of pre-operative anaemia with postoperative morbidity and mortality: an observational cohort study in patients undergoing emergency laparotomy --Manuscript Draft--

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<b>Abstract:</b>	Pre-operative anaemia is associated with poor outcomes after elective surgery, but its relationship to outcomes after emergency surgery is unclear. We analysed data from the National Emergency Laparotomy Audit from 1 <sup>st</sup> December 2013 to 30 <sup>th</sup> November 2017, excluding laparotomy for haemorrhage. Anaemia was classified as: 'mild' 129-110 g.l <sup>-1</sup> ; 'moderate' 109-80 g.l <sup>-1</sup> ; or 'severe' $\leq 79$ g.l <sup>-1</sup> . The primary outcome was 90-day mortality. Secondary outcomes were 30-day mortality, return to theatre and postoperative hospital stay. The primary outcome was available for 86,763 patients, of whom 45,306 (52%) were anaemic. There were 12,667 (15%) deaths at 90 postoperative days and 9246 (11%) deaths at 30 postoperative days. Anaemia was associated with increased 90-day and 30-day mortality, odds ratio (95% CI): mild, 1.15 (1.09-1.21); moderate, 1.44 (1.36-1.52); and severe, 1.42 (1.24-1.63), [A1] $p < 0.001$ for all; mild, 1.07 (1.00-1.12), $p = 0.030$ ; moderate, 1.30 (1.21-1.38), $p < 0.001$ ; and severe, 1.22 (1.05-1.43), $p = 0.010$ , respectively. All categories of anaemia were associated with prolonged hospital stay, adjusted coefficient (95% CI): mild, 1.31 (1.01-1.62); moderate, 3.41 (3.04-3.77); severe, 2.80 (1.83-3.77), $p < 0.001$ for all. Moderate and severe anaemia were associated with increased risk of return to theatre, odds ratio (95% CI): moderate 1.13 (1.06-1.21), $p < 0.001$ ; and severe 1.23 (1.06-1.43), $p = 0.006$ . Pre-operative anaemia is common in patients undergoing emergency laparotomy and is associated with increased postoperative mortality and morbidity.
<b>Response to Reviewers:</b>	Please see 'Response to reviewers' document, dated 08 February 2020.

Additional Information:	
Question	Response
Was written informed consent obtained for the study (and not just for anaesthesia/surgery, etc.) from all participants (including where skills are assessed in manikin studies), as detailed in the Instructions for Authors?	N/A
Research Ethics Committee approval for the study has been obtained.	Not applicable
Please confirm if any of the authors have competing interests data (e.g. personal, financial or academic). Please refer to the form at <a href="http://www.icmje.org/coi_disclosure.pdf">http://www.icmje.org/coi_disclosure.pdf</a> for examples of potential competing interests (though we do not require you to complete that form).	The authors DO have competing interests and confirm that I/we have included a statement headed 'Competing interests' at the end of my/our manuscript, stating any funding obtained and any potential competing interests, as detailed in the Guidance for Authors.
Is your manuscript a Clinical Trial?	No

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Dear John,

Thank you for your ongoing review of our manuscript. Enclosed is our revised manuscript. Below are our responses to your individual comments.

1) Please add numerical results (with statistical test results) to statements in the Summary (highlighted).

Response: These have now been added.

2) Please reorder reference 38 (I've moved it to just after reference 33 in the text).

Response: This has been reordered.

3) In Table 1 please enter the predicted values at 90 days.

Response: Predicted 90-day mortality is not available as the NELA risk model only provides predicted 30-day mortality.

4) In Table 2 I don't understand why 'Anti-hypertensive therapy' is a 'Cardiac sign'. I do not understand how it is mutually incompatible with the other subgroups under 'Cardiac sign'.

Response: These are categories of POSSUM's cardiac 'morbidity' variable. POSSUM variables were included in NELA's data collection proforma for the purposes of casemix adjustment (using P-POSSUM equation), and subsequently risk prediction.

5) I don't understand the p values in Table 5.

Response: We presume you mean Table 6 as these p values were highlighted in the revised manuscript you returned? Please let us know if otherwise. These p values were obtained from the Hosmer-Lemeshow statistical analysis. We have removed them from the Table but can re-insert them if needed. In addition, we have added 95% CIs for the area under curve ROC value. We have also noticed a minor error in the p values for the adjusted associations in Table 4 (highlighted). These have been corrected.

6) Please review the formatting requirements for figures. There should be no coloured surround. There should be no gridlines. The vertical axis label in Fig. 1 can be "Number of patients", not "Number of patients (N)". There should be no legend, for instance "Area under ROC curve = 0.8625" or the boxed legend in Fig. 3. There should be a label for all axes (Fig. 3 vertical axis). Axes labels should start with upper case: "Predicted mortality (proportion)". Please replace '.1' etc with '0.1' etc.

Response: Thank you. Fig. 1 has been re-formatted accordingly and the boxed legend removed from Fig. 2.

7) Can you generate a Giviti calibration belt instead of Fig. 3?

Response: A Giviti calibration belt has been generated and has now replaced the previous Figure 3. The legend has been updated accordingly in the main manuscript.

Please let us know if you require any further revisions or changes and thank you once again for your consideration.

Your sincerely,



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**The association of pre-operative anaemia with morbidity and mortality after emergency laparotomy**

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## Summary

Pre-operative anaemia is associated with poor outcomes after elective surgery, but its relationship to outcomes after emergency surgery is unclear. We analysed National Emergency Laparotomy Audit data from 1 December 2013 to 30 November 2017, excluding laparotomy for haemorrhage. Anaemia was classified as: 'mild' 129-110 g.l<sup>-1</sup>; 'moderate' 109-80 g.l<sup>-1</sup>; or 'severe'  $\leq 79$  g.l<sup>-1</sup>. The primary outcome was 90-day mortality. Secondary outcomes were 30-day mortality, return to theatre and postoperative hospital stay. The primary outcome was available for 86,763 patients, of whom 45,306 (52%) were anaemic. There were 12,667 (15%) deaths at 90 postoperative days and 9246 (11%) deaths at 30 postoperative days. Anaemia was associated with increased 90-day and 30-day mortality, odds ratio (95%CI): mild, 1.15 (1.09-1.21); moderate, 1.44 (1.36-1.52); and severe, 1.42 (1.24-1.63),  $p < 0.001$  for all; mild, 1.07 (1.00-1.12),  $p = 0.030$ ; moderate, 1.30 (1.21-1.38),  $p < 0.001$ ; and severe, 1.22 (1.05-1.43),  $p = 0.010$ , respectively. All categories of anaemia were associated with prolonged hospital stay, adjusted coefficient (95%CI): mild, 1.31 (1.01-1.62); moderate, 3.41 (3.04-3.77); severe, 2.80 (1.83-3.77),  $p < 0.001$  for all. Moderate and severe anaemia were associated with increased risk of return to theatre, odds ratio (95%CI): moderate 1.13 (1.06-1.21),  $p < 0.001$ ; and severe 1.23 (1.06-1.43),  $p = 0.006$ . Pre-operative anaemia is common in patients undergoing emergency laparotomy and is associated with increased postoperative mortality and morbidity.

## Introduction

Approximately 313 million operations are performed worldwide each year, after which at least 4 million (1%) people die within 30 postoperative days, accounting for 8% of all deaths [1, 2]. The rates of postoperative complications and morbidity are even higher [3]. The causes of poor postoperative outcomes are incompletely understood but include pre-existing co-morbidity, systemic inflammation and insufficient oxygen delivery to tissues [4-6]. Adequate oxygen delivery is dependent on cardiac output and arterial oxygen content. Low haemoglobin reduces arterial oxygen content and oxygen delivery for a given cardiac output.

Anaemia before elective surgery is present in 25-40% patients and it is associated with poor postoperative outcomes [7-9]. It remains unclear to what extent this association is causal. Despite this uncertainty, recent consensus statements strongly recommend investigating and treating anaemia before elective surgery, but it is less clear how these recommendations would apply to patients undergoing emergency surgery [10-12].

Approximately 11% of 30,000 patients who have an emergency laparotomy every year in England and Wales die within 30 days, with survivors discharged from hospital on average 15 days later [13, 14]. Patients who have emergency laparotomy are older than the patients who have scheduled laparotomy: they have multiple comorbidities and they may have concurrent infection, organ dysfunction or cancer, all of which contribute to anaemia [15]. Little is known about the associations between pre-operative anaemia and postoperative outcomes in patients undergoing emergency surgery. We hypothesised that pre-operative anaemia was associated with increased mortality and complications after emergency laparotomy.

## Methods

We used standard methods to report this secondary analysis of data submitted to the National Emergency Laparotomy Audit (NELA) between 1 December 2013 and 30 November 2017 [16-19]. This analysis was approved by the Health Care Quality Improvement Partnership.

Adults ( $\geq 18$  years) were eligible for inclusion in NELA if they had an expedited, urgent or emergency abdominal procedure on the gastrointestinal tract for conditions such as perforation, obstruction, ischaemia or abdominal abscess. We did not study patients who had laparotomy for acute bleeding or those with missing data. The primary outcome was all-cause mortality within 90 days of the index operation (Office for National Statistics death register). Secondary outcomes were 30-day mortality, return to theatre and postoperative length of stay in an acute hospital (for survivors).

We used the World Health Organization definitions of anaemia for men to categorise pre-operative haemoglobin concentrations for men and women: 'mild', 129-110 g.l<sup>-1</sup> 'moderate', 109-80

g.l<sup>-1</sup> and 'severe',  $\leq 79$  g.l<sup>-1</sup> [20, 21]. We analysed other pre-operative variables: age; sex; ASA physical status; surgical urgency; ECG abnormalities; cardiac signs; respiratory history; blood concentrations of urea, creatinine, sodium, potassium, white blood cells; heart rate; systolic blood pressure; and Glasgow Coma Scale (GCS) status. We also analysed intra-operative blood loss, peritoneal soiling, malignancy, operative severity, year of operation, number of operations during the index admission, grade of operating surgeon and anaesthetist and whether the patient was directly admitted to a critical care unit postoperatively.

We truncated continuous variables at the 1<sup>st</sup> and 99<sup>th</sup> percentile [22]. We log-transformed the skewed distributions of pre-operative serum creatinine and urea, which we then adjusted for non-linearity with a quadratic term that we also used for serum potassium, white blood cell count, heart rate and systolic blood pressure [13]. A fractional polynomial was used to transform the serum sodium distribution [13]. We categorised GCS: 3-8; 9-12; and 13-15.

We did not calculate a sample size for this secondary analysis. We used logistic regression to test the association of pre-operative haemoglobin concentration categories with mortality and return to theatre and linear regression to test their association with acute hospital length of stay. We also analysed haemoglobin values at a single threshold of  $< 130$  g.l<sup>-1</sup>. We then entered all other variables into multivariate models.

We used the area under the receiver-operating characteristic (ROC) curve to calculate the discrimination of death at 30 postoperative days by the NELA model and its calibration with the Hosmer-Lemeshow statistic. A GiViTI calibration belt was also generated to evaluate the NELA model's calibration. We report results for the whole cohort and patients categorised by; year of surgery, from 1<sup>st</sup> December to 30<sup>th</sup> November the next year (2013-4, 2014-5, 2015-6, 2016-7); [haemoglobin], 129-110 g.l<sup>-1</sup>, 109-80 g.l<sup>-1</sup>,  $\leq 79$  g.l<sup>-1</sup>. We used Stata for analyses (Version 15; StataCorp, College Station, TX, USA).

## Results

We analysed survival to 90 postoperative days for 86,763/95,844 (91%) patients, of whom 12,667 (14.5%) died (Table 1 and Supplementary Information Fig. S1). We analysed length of hospital stay for 77,389/95,844 (81%) patients.

There were 45,306/86,763 (52%) patients anaemic before laparotomy, with haemoglobin concentrations: 129-110 g.l<sup>-1</sup> in 24,901 (29%) patients; 109-80 g.l<sup>-1</sup> in 18,626 (21%) patients; and  $\leq 79$  g.l<sup>-1</sup> in 1779 (2%) patients (Fig. 1).

Mortality 90 days after surgery in patients who were anaemic and were not anaemic was 8064/45,306 (18%) and 4603/41,457 (11%), respectively. All categories of anaemia were associated with increased 90-day mortality on univariate analysis and these associations remained statistically



significant after adjustment (Table 2). Mortality 30 days after surgery was 9276 (11%), 5681/45,306 (13%) in anaemic patients. All categories of anaemia were associated with increased 30-day mortality on univariate analysis and these associations remained statistically significant after adjustment (Table 3).

The rate of unplanned return to theatre following emergency laparotomy was higher in patients with anaemia across all categories on univariate analysis. These associations remained statistically significant after adjustment only in patients with moderate and severe anaemia (Table 4). Pre-operative anaemia was associated with prolonged postoperative hospital stay when compared to patients without anaemia. These associations remained statistically significant across all categories after adjustment (Table 5).

The discrimination and calibration of the NELA risk model are displayed in Table 6 and Figures 2 and 3.

## **Discussion**

We found that about half the patients who had emergency laparotomy were anaemic, which was associated with mortality 30 days and 90 days later and unplanned return to theatre and length of hospital stay.

We have completed the first validation of the NELA risk model, which was derived from 38,830 patients who had an emergency laparotomy between December 2013 and November 2015. The calibration of the model was good across all levels of risk and over time despite changes in the inclusion and exclusion criteria of the NELA dataset.

The association of pre-operative anaemia with adverse clinical outcomes after scheduled surgery has been thoroughly described, but not after unscheduled surgery. A retrospective study reported that 61% of 310,311 US Veterans were anaemic before emergency major noncardiac surgery, but did not report clinical outcomes. Pre-operative anaemia has been associated with increased mortality after repair of hip fracture [24].

It remains unclear if the association of anaemia with poor outcomes is causal or not [25, 26]. We postulate that the association with mortality at 30 postoperative days is more likely to be causative than mortality at 90 days, which we think is likely to be associated with underlying disease. If so, targeted management of anaemia is more likely to reduce morbidity and mortality at 30 days than 90 days.

We think that our findings are likely to be generalisable, at least within the United Kingdom, due to national patient coverage over multiple years with rigorous data collection, linked with externally validated mortality data. We also opted to use contemporary definitions of anaemia in

view of recent work suggesting that traditional WHO thresholds may lead to under-diagnosis of anaemia in women [21].

Our study is limited by unidentified factors that may be associated with both pre-operative anaemia and outcomes. We were unable to adjust for peri-operative red blood cell transfusion, which is not recorded by NELA. The haemoglobin concentration at the time of emergency laparotomy is not known as the NELA database does not detail when pre-operative haemoglobin concentration was measured. We did not analyse the association of postoperative haemoglobin concentrations with outcomes as they were not recorded for 25% of the patients. We could not explore the causes of anaemia and its varying associations with morbidity and mortality over time. The causes of death were not available to us.

The widespread adoption of restrictive transfusion practices is associated with more patients being discharged anaemic from hospital [27]. Prospective studies, addressing the limitations identified from our work, are already underway [28]. A recent scoping review found evidence of poor reporting of patient-centred outcomes in anaemia management studies [29], although data are beginning to emerge on the effects of anaemia management on quality of life [30].

There is no consensus on the peri-operative management of anaemic emergency surgery patients, for instance with treatments such as iron and erythropoietin, although haematinics are recommended by some expert panels [11, 12]. There is an uncertain effect of iron infusions on infection, whilst red blood cell transfusion is associated with harm [31-34]. Newer markers of iron status, such as hepcidin, may help predict which patients will respond to intravenous iron [35-37]. A combination of intravenous iron, erythropoietin, B12 and folic acid given to patients within 24 h of elective cardiac surgery reduced red blood cell transfusion in the first seven postoperative days [38]. This and similar treatments should be investigated in the NELA population.

In conclusion, pre-operative anaemia is common in patients who have an emergency laparotomy and is associated with increased 90-day mortality, unplanned return to theatre and postoperative hospital length of stay. Further research is needed to determine whether investigation and targeted peri-operative treatment of anaemia in this high-risk patient cohort may act to improve outcomes.

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**Table 1** Characteristics of 86,763 patients who had emergency laparotomy, categorised by pre-operative haemoglobin (Hb) concentration. Values are median (IQR [range]) or number (proportion). Values may not sum to 100% due to rounding

	Pre-operative [Hb]; g.l <sup>-1</sup>			
	≥ 130 (n = 41,457)	129-110 (n = 24,901)	109-80 (n = 18,626)	≤ 79 (n = 1779)
Age; years	66 (52-76 [18-103])	69 (55-79 [18-105])	69 (55-78 [18-102])	65 (49-75 [18-100])
Hb; g.l <sup>-1</sup>	145 (137-155 [130-250])	120 (115-125 [110-129])	99 (92-105 [80-109])	72 (68-74 [40-79])
Male	22,898 (55%)	9895 (40%)	7882 (42%)	831 (47%)
ASA physical status				
1	5861 (14%)	1951 (8%)	876 (5%)	99 (6%)
2	16,343 (39%)	8802 (36%)	5057 (27%)	420 (24%)
3	13,002 (31%)	9617 (39%)	7833 (42%)	628 (35%)
4	5638 (14%)	4189 (17%)	4379 (24%)	547 (31%)
5	613 (2%)	342 (1%)	481 (3%)	85 (5%)
Both consultants in theatre	28,447 (69%)	18,404 (74%)	14,358 (77%)	1429 (80%)
Return to theatre	3027 (7%)	1966 (8%)	2022 (11%)	250 (14%)
Mortality				
30 days				
Observed	3595 (9%)	2596 (10%)	2767 (15%)	318 (18%)
Predicted	9%	11%	13%	16%
90 days				
Observed	4603 (11%)	3677 (15%)	3953 (21%)	434 (24%)
	n = 38,119	n = 22,333	n = 15,552	n = 1385
Days in hospital	10 (6-17 [1-421])	12 (7-20 [1-584])	15 (9-26 [1-446])	15 (9-28 [2-220])



**Table 2** Odds ratios (95%CI) for the associations of pre-operative and intra-operative variables with 12,667 deaths within 90 days of emergency laparotomy in 86,763 patients.

Variable	Univariate		Multivariate	
	OR (95%CI)	p value	OR	p value
<b>Pre-operative</b>				
<b>Haemoglobin; g.l<sup>-1</sup></b>				
> 129	Reference		Reference	
110-129	1.38 (1.32-1.45)	< 0.001	1.15 (1.09-1.21)	< 0.001
80-109	2.15 (2.05-2.26)	< 0.001	1.44 (1.36-1.52)	< 0.001
≤ 79	2.58 (2.31-2.89)	< 0.001	1.42 (1.24-1.63)	< 0.001
Age	1.04 (1.04-1.05)	< 0.001	1.04 (1.03-1.04)	< 0.001
Female	0.99 (0.95-1.03)	0.281	1.02 (0.97-1.07)	0.48
<b>ASA</b>				
1-2	Reference		Reference	
3	4.15 (3.91-4.41)	< 0.001	2.06 (1.93-2.20)	< 0.001
4	14.4 (13.6-15.3)	< 0.001	4.06 (3.77-4.38)	< 0.001
5	46.5 (41.3-52.3)	< 0.001	8.43 (7.32-9.71)	< 0.001
<b>Urgency of surgery; h</b>				
18-24	Reference		Reference	
6-18	0.87 (0.82-0.93)	< 0.001	0.85 (0.79-0.92)	< 0.001
2-6	1.36 (1.28-1.45)	< 0.001	0.97 (0.89-1.04)	< 0.001
< 2	3.43 (3.21-3.67)	< 0.001	1.42 (1.29-1.55)	< 0.001
<b>ECG</b>				
No abnormalities	Reference		Reference	
AF rate 60-90	2.44 (2.25-2.64)	< 0.001	1.19 (1.09-1.31)	< 0.001
Other	3.11 (2.97-3.25)	< 0.001	1.14 (1.08-1.21)	< 0.001
<b>Cardiac sign</b>				
Normal	Reference		Reference	
Anti-hypertensive therapy	2.20 (2.10-2.29)	< 0.001	1.02 (0.97-1.08)	0.38
Borderline cardiomegaly	4.13 (3.85-4.42)	< 0.001	1.26 (1.15-1.37)	< 0.001
Cardiomegaly	5.57 (4.90-6.32)	< 0.001	1.26 (1.08-1.46)	0.003
Heart rate	1.02 (1.02-1.02)	< 0.001	1.01 (1.00-1.01)	< 0.001
Systolic blood pressure	0.98 (0.98-0.98)	< 0.001	0.99 (0.99-1.00)	< 0.001
<b>Respiratory</b>				
No dyspnoea	Reference		Reference	
Dyspnoea on exertion	2.46 (2.32-2.58)	< 0.001	1.29 (1.22-1.37)	< 0.001
Dyspnoea < one stair flight	3.87 (3.66-4.10)	< 0.001	1.58 (1.47-1.69)	< 0.001
Dyspnoea at rest	5.64 (5.21-6.11)	< 0.001	1.65 (1.49-1.82)	< 0.001
<b>Blood results</b>				
Creatinine	2.82 (2.72-2.93)	< 0.001	1.27 (1.20-1.35)	< 0.001
Sodium	1.00 (0.99-1.00)	0.422	1.00 (1.00-1.01)	< 0.001
Potassium	1.38 (1.34-1.43)	< 0.001	1.21 (1.16-1.25)	< 0.001
Urea	2.68 (2.60-2.76)	< 0.001	1.38 (1.32-1.46)	< 0.001
White blood cell count	1.02 (1.02-1.03)	< 0.001	1.00 (0.99-1.00)	0.54
<b>Glasgow Coma Score</b>				
13-15	Reference		Reference	
9-12	5.88 (5.02-6.90)	< 0.001	1.84 (1.51-2.22)	< 0.001
3-8	7.76 (6.98-8.62)	< 0.001	2.23 (1.96-2.54)	< 0.001
<b>Intra-operative</b>				
<b>Peritoneal soiling</b>				

<b>None</b>	Reference		Reference	
<b>Serous fluid</b>	1.38 (1.31-1.45)	< 0.001	1.10 (1.03-1.16)	0.001
<b>Localised pus</b>	0.82 (0.75-0.88)	< 0.001	0.89 (0.81-0.98)	0.012
<b>Pus, blood or bowel content</b>	2.10 (2.00-2.20)	< 0.001	1.33 (1.25-1.42)	< 0.001
<b>Blood loss; ml</b>				
<b>&lt;100</b>	Reference		Reference	
<b>101-500</b>	1.29 (1.24-1.35)	< 0.001	1.05 (1.00-1.10)	0.074
<b>501-1000</b>	1.75 (1.61-1.92)	< 0.001	1.15 (1.03-1.27)	0.010
<b>&gt;1000</b>	2.79 (2.42-3.23)	< 0.001	1.85 (1.54-2.21)	< 0.001
<b>Malignancy status</b>				
<b>None</b>	Reference		Reference	
<b>Primary only</b>	1.06 (0.99-1.13)	0.063	1.31 (1.22-1.41)	< 0.001
<b>Nodal metastases</b>	1.66 (1.53-1.80)	< 0.001	2.43 (2.20-2.69)	< 0.001
<b>Distant metastases</b>	3.97 (3.75-4.20)	< 0.001	6.45 (6.02-6.92)	< 0.001
<b>Consultant in theatre</b>				
<b>Surgeon</b>	1.37 (1.28-1.46)	< 0.001	1.06 (0.98-1.14)	0.094
<b>Anaesthetist</b>	1.59 (1.51-1.68)	< 0.001	1.03 (0.97-1.09)	0.29
<b>ICU admission from theatre</b>	3.06 (2.91-3.20)	< 0.001	1.05 (0.99-1.11)	0.088

AF, atrial fibrillation; ASA, ASA physical status; COAD, chronic obstructive airways disease; ICU, intensive care unit.

**Table 3** Odds ratios (95%CI) for the associations of pre-operative anaemia with 9276 deaths within 30 days of emergency laparotomy in 86,763 patients.

	Univariate		Multivariate	
	OR (95%CI)	p value	OR (95%CI)	p value
<b>Haemoglobin; g.l<sup>-1</sup></b>				
<b>&gt; 129</b>	Reference		Reference	
<b>110-129</b>	1.22 (1.16-1.29)	< 0.001	1.07 (1.00-1.12)	0.030
<b>80-109</b>	1.83 (1.74-1.94)	< 0.001	1.30 (1.21-1.38)	< 0.001
<b>≤ 79</b>	2.29 (2.02-2.60)	< 0.001	1.22 (1.05-1.43)	0.010

**Table 4** Odds ratios (95% CI) for the associations of pre-operative anaemia with return to theatre after emergency laparotomy in 86,763 patients .

	Univariate		Multivariate	
	OR (95%CI)	p value	OR (95%CI)	p value
<b>Haemoglobin; g.l<sup>-1</sup></b>				
<b>&gt; 129</b>	Reference		Reference	
<b>110-129</b>	1.09 (1.02-1.15)	0.004	1.02 (0.96-1.09)	0.472
<b>80-109</b>	1.55 (1.46-1.65)	< 0.001	1.13 (1.06-1.21)	< 0.001
<b>≤ 79</b>	2.10 (1.83-2.42)	< 0.001	1.23 (1.06-1.43)	0.006

**Table 5** Linear regression for the associations of pre-operative anaemia with hospital stay after emergency laparotomy in 86,763 patients

	Univariate		Multivariate	
	Coefficient (95%CI)	p value	Coefficient (95%CI)	p value
<b>Haemoglobin; g.l<sup>-1</sup></b>				
<b>&gt; 129</b>	Reference		Reference	
<b>110-129</b>	2.57 (2.25-2.89)	< 0.001	1.31 (1.01-1.62)	< 0.001
<b>80-109</b>	6.65 (6.29-7.01)	< 0.001	3.41 (3.04-3.77)	< 0.001
<b>≤ 79</b>	7.87 (6.83-8.90)	< 0.001	2.80 (1.83-3.77)	< 0.001

**Table 6** Performance of the National Emergency Laparotomy Audit (NELA) risk model in the study cohort, categorised by NELA year and anaemia category

Study group	Area under ROC curve (95% CI)	Overall Hosmer-Lemeshow $\chi^2$
<b>Whole study cohort</b>	0.863 (0.858 – 0.866)	71.6
<b>Year of NELA</b>		
<b>2013-4</b>	0.861 (0.853 – 0.867)	23.3
<b>2014-5</b>	0.867 (0.860 – 0.873)	29.1
<b>2015-6</b>	0.856 (0.851 – 0.865)	21.8
<b>2016-7</b>	0.863 (0.855 – 0.869)	33.0
<b>Haemoglobin; g.l<sup>-1</sup></b>		
<b>&gt; 129</b>	0.880 (0.874 – 0.885)	57.1
<b>110-129</b>	0.851 (0.843 – 0.857)	20.5
<b>80-109</b>	0.836 (0.828 – 0.843)	61.4
<b>≤ 79</b>	0.826 (0.803 – 0.848)	25.4

ROC, receiver operator characteristic

**Figure 1** Histogram representing distribution of pre-operative haemoglobin in patients undergoing emergency laparotomy.

**Figure 2** Receiver operator characteristic curve of the NELA risk tool versus 30-day mortality.

**Figure 3** Giviti calibration belt comparing the observed 30-day mortality (vertical axis) against the predicted NELA risk tool mortality (horizontal axis). Predicted rates calibrated well with observed rates. The red line is the unitary tangent, the light grey are 95% CI and the dark grey are 99% CI.

**Supplementary Figure 1** STROBE flow diagram of patients included and excluded from analysis.

Figure 1

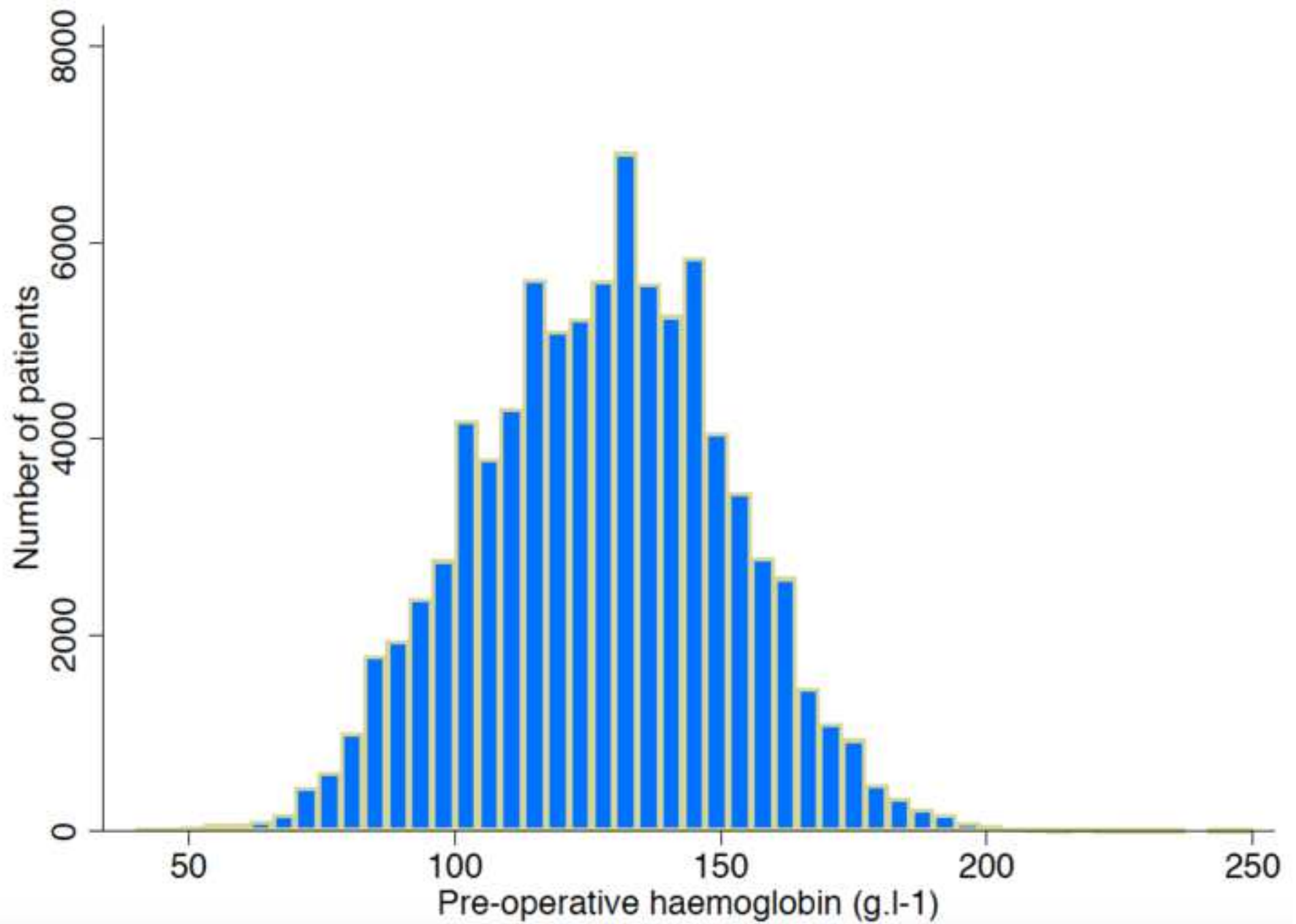




Figure 2

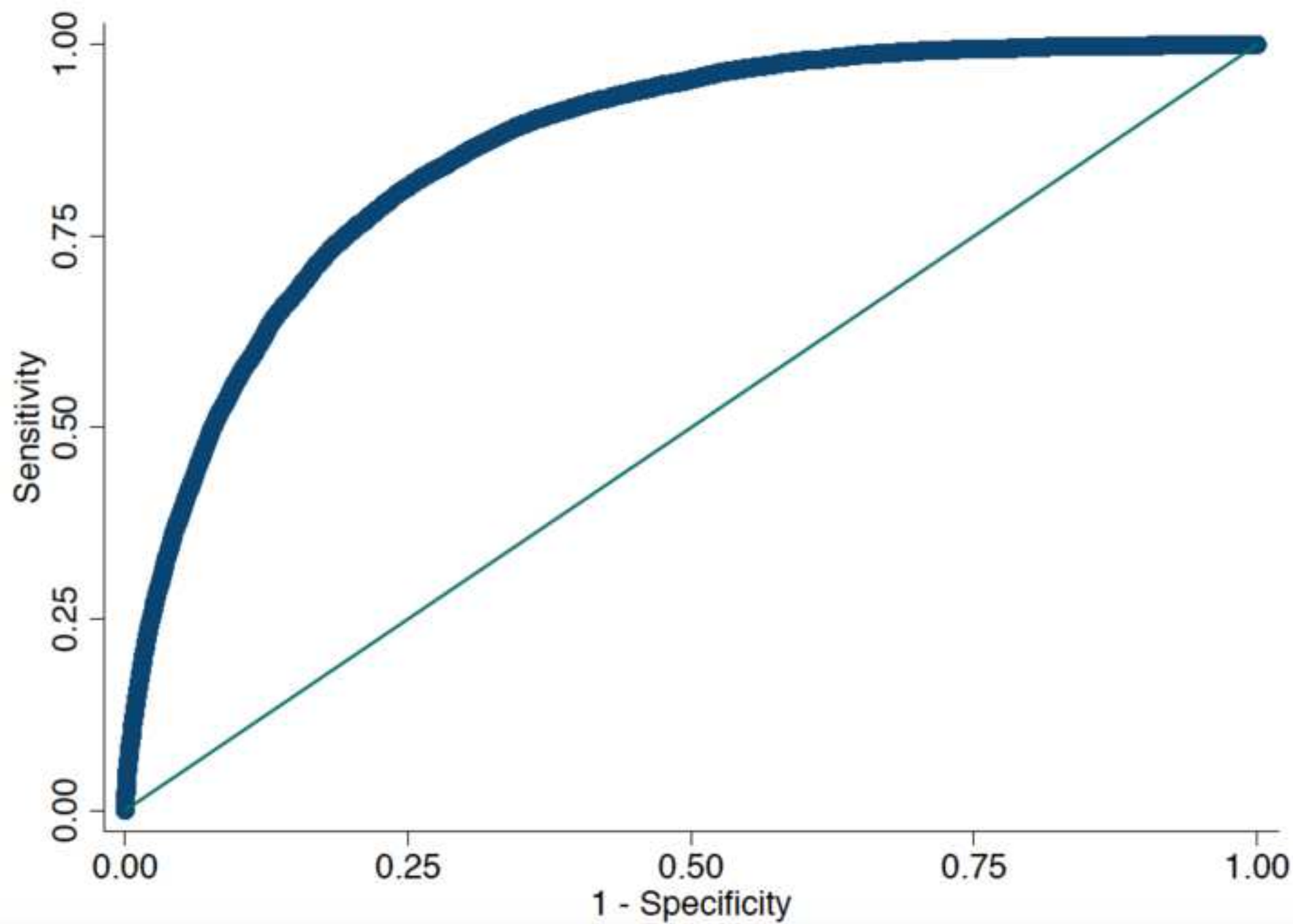
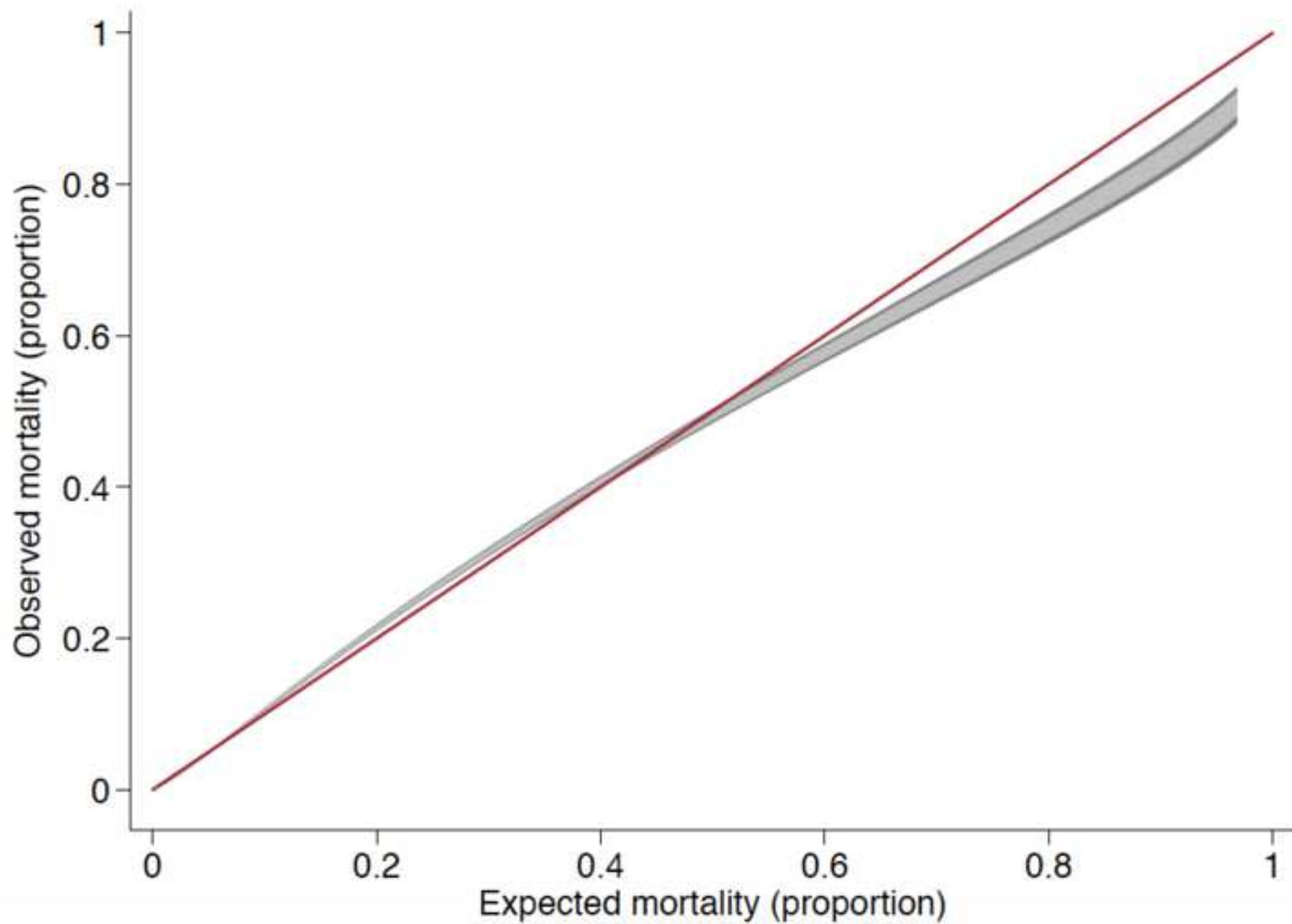


Figure 3



STROBE Statement—Checklist of items that should be included in reports of *observational studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4, 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, 5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5, 6
		(b) Describe any methods used to examine subgroups and interactions	5, 6
		(c) Explain how missing data were addressed	5, 6
		(d) If applicable, explain how loss to follow-up was addressed	5, 6
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	Suppl. Figure 1
		(c) Consider use of a flow diagram	Suppl.

			Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Suppl. Figure 1
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6, 7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 7, Tables 1 to 6
		(b) Report category boundaries when continuous variables were categorized	6, 7
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8, 9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7, 9
Generalisability	21	Discuss the generalisability (external validity) of the study results	7, 8
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

**Supplementary Figure 1.** STROBE flow diagram of patients included and excluded from analysis.