Development and Validation of a Score to Predict Postoperative Respiratory Failure in a Prospective Multicentre European Cohort

Running head**: Prediction of Postoperative Respiratory Failure**

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Financial support: The PERISCOPE study was funded and supported through the European Society of Anaesthesiology's Clinical Trials Network.

Word count: Abstract 278, Manuscript 3190.

Abstract

Background: Postoperative respiratory failure (PRF) is the most frequent respiratory complication after surgery.

Objective: To build a clinically useful predictive model for PRF.

Design: Prospective observational study of a multicentre cohort.

Setting: Sixty-three hospitals across Europe.

Patients: Patients undergoing all surgical procedures under general or regional anaesthesia during 7-day recruitment periods.

Main outcome measures: Development of PRF within 5 days of surgery. PRF was defined by a partial pressure of oxygen in arterial blood (PaO_2) < 60 mmHg or new-onset oxyhaemoglobin saturation measured by pulse oximetry (SpO_2) < 90% in room air requiring conventional oxygen therapy, or noninvasive or invasive mechanical ventilation.

Results: PRF developed in 224 (4.2% of the 5384 patients studied). In-hospital mortality was higher in patients with PRF (10.3%; 95% confidence interval [CI], 6.3%–14.3%) than in those without PRF (0.4%; 95% CI, 0.2%–0.6%). Regression modelling identified a predictive PRF score including 7 independent risk factors: low preoperative SpO_2, at least 1 preoperative respiratory symptom, preoperative chronic liver disease, history of congestive heart failure, open intrathoracic or upper abdominal surgery, surgical procedure lasting at least 2 hours, and emergency surgery. The area under the receiver operating characteristic curve (*c*-statistic) was 0.82 (95% CI, 0.79–0.85) and the Hosmer-Lemeshow goodness-of-fit statistic was 7.08 (P =0.253).

Limitations: Follow-up ended at hospital discharge, the cohort was recruited by volunteer hospitals that did not cover all of Europe, and external validation of the index was not performed.

Conclusions: A risk score based on 7 objective, easily assessed factors was able to predict which patients would develop PRF. The score can potentially facilitate preoperative risk assessment and management and provide a basis for testing interventions to improve outcomes.

The study was registered at ClinicalTrials.gov (identifier, NCT01346709).

Introduction

Postoperative respiratory failure (PRF) is the most frequent postoperative pulmonary complication (PPC) with major impact on outcome and health costs.[1-7] The pathogenesis of PRF depends on factors related to patient status as well as anaesthetic and surgical procedure.[8-10] The incidence of PRF in general surgical populations ranges between 0.2% and 3.4%[8] and several scores for predicting PRF have been proposed.[1, 3-7, 11] However, previous studies developing scores to predict PRF defined this complication differently. Definitions that have been used include unexpected reintubation, [1, 5, 7, 11] need for postoperative mechanical ventilation[1, 3] or postoperative acute lung injury and acute respiratory distress syndrome (ALI/ARDS).[4, 6] In addition, most of the scores available have been developed with retrospective databases that contain administrative information and coding.[1, 3, 5-7, 11] Retrospectively identified predictors have certain limitations,[12-15] including low positive predictive values and moderate reliability, and they are subject to errors in data collection, higher percentages of missing values, and lack of information on variables of clinical interest.

Current thinking on the diagnosis of PRF calls for using objective measures of newly developing hypoxaemia detected during the postoperative course:[8] specifically, partial pressure of oxygen in arterial blood (PaO_2) must be less than 60 mmHg, a condition that normally corresponds to arterial oxygen saturation less than 90%. Furthermore, according to the most recent international consensus on ARDS, the severity of PRF may be further classified as mild, moderate, or severe based on the ratio of PaO_2 to the inspiratory oxygen fraction (FIO_2).[16] Stratifying risk for different degrees of

PRF severity would potentially facilitate early detection and management of this complication.

In this study, we used a large European database of general surgery cases (PERISCOPE cohort – Prospective Evaluation of a RIsk Score for postoperative pulmonary COmPlications in Europe)[17] created to externally validate the ARISCAT risk score for a PPC composite. Hypothesising that it would be possible to use the PERISCOPE data to build a simple risk score to predict PRF alone, we designed the present secondary analysis. Our aims were to identify perioperative risk factors for PRF and build and internally validate a specific predictive model. We also stratified PRF at 3 levels of severity based on the presence of hypoxaemia and type of respiratory support in order to assess differences in outcome.

Methods

Study Design

A cohort of surgical patients was created for the observational multicentre PERISCOPE study. Sixty-three European hospitals (see appendix) recruited patients during continuous 7-day periods, choosing a convenient date to begin data collection between 2 May and 15 August 2011. Follow-up ended in November 2011. The participating hospitals constituted a convenience sample of volunteer centres found through the European Society of Anaesthesiology (ESA); candidates were approached directly by national study coordinators. The study was registered at ClinicalTrials.gov (identifier, NCT01346709).

PERISCOPE Cohort Inclusion and Exclusion Criteria

Consecutive patients undergoing nonobstetric in-hospital elective or emergent surgery under general (including combined general anaesthesia) or regional (neuroaxial or plexus) anaesthesia were recruited.

Exclusion criteria were age under 18 years; obstetric procedures or any procedure during pregnancy; procedures in which only local or peripheral nerve anaesthesia would be used; procedures outside an operating theatre; procedures related to a previous postoperative complication; organ transplantation; patients with preoperatively intubated trachea; and outpatient procedures, defined as those requiring a hospital stay of less than 24 hours.

Ethical Considerations

Ethics requirements differed in the 21 countries, but formal approval from a research ethics review board was applied for and given in each: the locally responsible investigator applied for and obtained approval from the ethics committee of each participating hospital. Written informed consent was obtained from each patient.

Organisation, Data Collection and Quality Assurance

The research team consisted of a steering committee and nationally and locally responsible investigators, who were all anaesthesiologists. Data collectors, who did not modify a centre's customary management of patients, used a structured questionnaire to record the following information: administrative data (dates of surgery and discharge; status — alive or dead — at discharge), general information (sex, birth date, height, and weight), preoperative variables (oxyhaemoglobin saturation measured by pulse oximetry [SpO_2] breathing air in supine position after 1 minute resting breathing air, or in patients on oxygen, SpO_2 after 10 minutes without oxygen; respiratory symptoms based on a simplified version of the Medical Research Council questionnaire;[18] respiratory infection in the last month; haemoglobin concentration; cough test; chronic pulmonary disease; smoking status; and the American Society of Anesthesiologists [ASA] class), and intraoperative variables (surgical incision, surgical duration in hours, type of surgery [scheduled or emergent], description of procedure, surgical specialty and anaesthetic technique). Definitions of all variables are in the online supplement (Supplementary Table 1).

The data collectors also sought all PPCs by searching medical records daily to find relevant events until hospital discharge; information on PRF was thus recorded as this complication developed throughout the hospital stay. Data were collected on paper forms and then transferred anonymously to secure online case records (OpenClinica, Boston, MA). This electronic system incorporated quality control algorithms to validate online data entry and identify missing data. An off-site data manager checked entries to confirm completeness and asked the local team contact to provide additional information if necessary. An expert on the International Classification of Diseases, Ninth Revision, Clinical Modification, coded all diagnoses and procedures at the end of the collection period.

Outcomes

The primary outcome of interest for this secondary analysis was PRF defined as new-onset hypoxaemia appearing within 5 postoperative days at 3 levels of severity: mild (PaO_2<60 mmHg or SpO_2<90% in room air but responding to mask/nasal supplemental oxygen); moderate (necessitating noninvasive or invasive mechanical ventilation to treat a PaO_2<60 mmHg or SpO_2<90%); or severe (requiring invasive mechanical ventilation to manage a PaO_2/FiO_2<200 mmHg regardless the level of positive end-expiratory pressure [PEEP]). Hypoventilation due to residual effects of anaesthetics or opiates and heart failure were ruled out in all cases.

Secondary outcomes of interest were postoperative intensive care unit (ICU) admission, postoperative length of stay (LOS), and in-hospital mortality.

Statistical Analysis

The size of the PERISCOPE cohort had been calculated to provide at least 10 events per variable we expected to enter the logistic regression model.[19] It was estimated that the 63 PERISCOPE centres would be able to collect around 5000 cases and that the incidence of PRF would be around 3%.[1, 2, 20, 21] Recording at least 150 PRF events would allow around 15 predictor variables to be entered into logistic regression. Demographic and clinical characteristics are expressed in percentages and medians and interquartile ranges (IQR).

Potential PRF predictors were selected according to the investigators' consensus on measurable preoperative variables or the results of previous studies.[2, 22]. Independent continuous variables (age, SpO_2, and duration of surgery) were grouped into categories based on the investigators' understanding of relevant clinical cut points.

Unadjusted associations between all categorical variables and PRF were evaluated with the chi-square test or the Fisher exact test, as appropriate. Bivariate odds ratios (ORs) and 95% confidence intervals (CIs) were also estimated. The possibility of colinearity between categorical variables was tested with the Cramer V test (nominal variables) or Kendall's tau-b (ordinal variables).

The logistic regression model was constructed using a backward stepwise selection procedure in which the presence of PRF was the dependent variable. Independent predictors were entered into the model if a significant association ($P<0.05$) was identified on bivariate analysis and the correlation

coefficient between them (colinearity) was less than 0.25. Potential predictors were removed if this exclusion did not result in a significant change in the log-likelihood ratio test. The cutoff for variable removal was set at a significance level of 0.05. Adjusted ORs and 95% CIs were also calculated.

To avoid overfitting and obtain reliable internal validation of the subset of factors, we used a bootstrap method,[23] deriving 1000 computer-generated samples by random selection with replacement, each including the same number of patients. Within each bootstrap sample, the β coefficient was calculated using all selected independent variables. The robustness of the model and, thus, the reliability of predictor variables in the final regression model were estimated by the 95% CI of the β coefficient derived from the bootstrap samples.

A simplified predictive risk score for clinical use was then calculated by multiplying each β coefficient (corrected after bootstrapping) by 10 and rounding to the nearest integer. The integers were added together to produce an overall PRF risk score for each patient. To evaluate the ability of the score to predict increasing PRF risk, we used the minimum description length principle[24] to divide the sample into 3 risk levels, each with a similar number of patients. The logistic regression model's calibration was then assessed by the Hosmer-Lemeshow goodness-of-fit statistic and by plotting the actual frequency of PRF in each of the 3 risk levels against the predicted probability of PRF in that risk group.

To assess the ability of the simplified PRF risk score to discriminate between patients with and without PRF we used the *c*-statistic, which was also displayed graphically as the area under the receiver operating characteristic

curve. Additionally, to check the performance of the model if it were used without information for any single factor such as SpO_2, which might not be recorded in all centres, we also checked the discriminative performance by calculating the c-statistics and calibration statistics for alternative 6-factor models.

The Mann-Whitney *U* test was used to compare postoperative LOS between patients with and without PRF. An actuarial life table was constructed to assess in-hospital mortality after development of mild, moderate, or severe PRF. The Wilcoxon-Gehan test was used to compare overall survival curves.

Statistical analyses were performed using the SPSS software package (version 20.0; IBM Corp., Armonk, NY). Bootstrapping was performed using R, version 3.0.2 (R Project for Statistical Computing).

Results

Of 5859 initially eligible patients, 5384 (91.9%) were included in the final analysis (see Figure 1). The characteristics of patients and procedures are detailed in Table 1.

PRF developed in 224 patients (4.2% of the cohort) and was classified as mild in 155 (2.9%), moderate in 43 (0.8%), and severe in 26 (0.5%). The time between surgery and the onset of PRF was a median of 0.5 days (IQR, 1 day). In 54.9% of the patients with PRF, symptoms began within 24 hours; in 94.6% onset was within 3 days.

PRF, ICU Stay, Postoperative LOS, and Mortality

ICU admission was required in 181 (80.8%) of the patients who developed PRF and in 318 (6.2%) of the patients who did not. The ICU stay was significantly longer in patients who developed PRF ($P<0.001$); these patients were in the unit a median of 44 (72.5) hours whereas the median stay for patients without PRF was 22 (34) hours.

The median in-hospital postoperative stay was also longer in patients with PRF (9 [9] days) than in those without PRF (4 [5] days) ($P<0.001$). Forty-six patients died in the hospital; 23 of them had PRF (10.3% of the 224 patients with PRF) and 23 did not (0.44% of the 5160 without PRF) ($P<0.001$). Figure 2 shows survival curves for in-hospital mortality according to PRF severity. Differences in hospital mortality between PRF severity levels were statistically significant ($P<0.001$).

Risk Factors and PRF Score

The independent variables entered into logistic regression are shown in Table 2, along with variables that were not significant on bivariate analysis or that were significant but rejected because of high colinearity with other variables. Multivariable logistic regression selected 7 independent predictors of PRF: 4 were related to the patient's presurgical health status (low preoperative SpO_2 in air, respiratory symptoms, heart failure, and chronic liver disease) and 3 were procedure-related (open thoracic or abdominal surgery, duration, and emergency surgery). All were retained in more than 95% of the bootstrap subsamples. Table 3 shows the ORs for these predictors. The 7-variable regression model had good discrimination (*c*-statistic, 0.82) and calibration (Hosmer-Lemeshow P=0.253). The area under the receiver operating characteristic curve (*c*-statistic) and calibration plot are presented in Figure 3. Supplementary Table 2 shows the statistics reflecting the performance of the model without inclusion of preoperative SpO_2 or any other single factor; the *c*-statistic fell to 0.81 for that model and all other alternative 6-variable models created by removing one of the factors.

The incidence of PRF increased significantly between risk levels (low, <12; intermediate; 12–22; and high, ≥23 points). The incidences (95% CIs) were 1.1% (0.7%–1.5%), 4.6% (3.4%–5.6%) and 18.8% (15.8%–21.8%), respectively, for each level. Table 4 shows sensitivity, specificity and other statistics assessing the predictive utility of the cutoffs for moderate risk (≥ 12 points) and high risk (≥ 23 points).

Discussion

The incidence of PRF in this prospective, multicentre surgical cohort receiving general or regional anaesthesia was 4.2%, and risk was predicted by a score based on 7 easily recorded predictors. The PERISCOPE-PRF score performed well, as it was able to identify 82% of the patients who would develop PRF (as shown by the *c*-statistic of 0.82), and it was able to distinguish 3 levels of risk. Calibration measures showed good agreement between the predicted and observed values within the risk levels; bootstrapping confirmed the stability of the dataset and all 7 predictors were retained after the procedure. PRF significantly increased the ICU admission rate, postoperative LOS, and in-hospital mortality.

Several studies of risk have defined a composite PPC as the primary outcome.[2, 22, 25, 26] The complications most often included are respiratory infection, bronchospasm, PRF, atelectasis, and pleural effusion among others. While such an approach to risk modelling is useful for guiding preoperative management and vigilance, clinicians are aware that the pathogenesis and clinical impact of each component in the composite is substantially different. We therefore designed the present study to determine whether the PERISCOPE model, also designed to predict a composite, could be used to predict only PRF.

Most previous studies of PRF defined this complication as the need for more than 48 hours of mechanical ventilation or unplanned reintubation,[1, 3, 5, 7, 11] which would only identify the most severe forms of PRF. The predictive scores for PRF developed in these studies showed *c*-statistics ranging from 0.79[11] to 0.89[3]. The *c*-statistic of 0.82 for the PERISCOPE-PRF score fell

within this range and is consistent with those earlier findings in spite of differences in definitions or design.

The incidence of PRF in this cohort (4.2%) was higher than previous rates, which ranged from 2.6% to 3.4%.[1, 8, 20] There are important methodological, population and outcome definition differences between our study and the earlier ones that can account for the higher rate. Our definition of PRF specified that new-onset hypoxaemia of noncardiac cause must have appeared within 5 postoperative days, marked objectively by a level of SpO_2 < 90% breathing air, which corresponds approximately to a ratio of PaO_2/FIO_2 < 300. There is no consensus about the postoperative period within which a PPC can be considered attributable to surgery.[8] Several studies analysed PRF developing within 30 days,[1, 3, 11] whereas others limited the time frame to 3 to 7 days.[4-7] We chose a 5-day period so that the complication and the surgical-anaesthetic events would be clearly linked, thereby excluding 8.9% of the PERISCOPE patients who later developed this complication. Although we included patients without previous lung injury and lacked information to calculate the PaO_2/FIO_2 ratio for all patients, we did classify PRF in 3 levels of severity, in a way that was similar to the recent ARDS classification.[16] Our stratification was based on the presence of hypoxaemia and the kind of respiratory support required to manage it (conventional oxygen therapy and noninvasive or invasive mechanical ventilation regardless of PEEP level), a classification consistent with current clinical management of PRF. Up to 74% of these patients can be managed with noninvasive ventilation,[27] which several studies have found very effective for treating even severe levels of hypoxaemia.[28-31] Recently, Kor *et al*[4] found a 2.6% incidence of ALI in patients undergoing

high-risk surgery using a similar definition of impaired oxygen exchange ($PaO_2/FIO_2 < 300$), but their definition required the presence of pulmonary infiltrates as well. It is likely that the higher PRF incidence in our study was due to the fact that the measurable criterion was arterial oxygenation (SpO_2). The incidence of severe PRF in our study ($PaO_2/FIO_2 < 200$ regardless of PEEP level) was 0.5%, similar to previous studies.[6] However, because of the multicentre nature of our study, we cannot rule out that local clinical practices might have led to differences in the distribution of PRF severity. Practices might even have contributed to preventing the development of PRF, or variations in resources might have led to higher rates of rescue failure[32] in some centres. However, we think it is important for the clinician to note that all levels of postoperative hypoxaemia severity had an impact on mortality in this cohort (Figure 2), a finding which confirms that PRF prediction overall is of great importance.

Four of the 7 predictors of PRF risk we identified were related to the patient's health status and these factors accounted for 57% of the total risk. To our knowledge, this is the first study reporting that low preoperative SpO_2 breathing air and even a single respiratory symptom are strongly associated with risk for PRF, although slight oxygen desaturation ($SpO_2 \leq 95\%$) has been found to be an independent predictor of a composite PPC outcome.[2] Additionally, clinical prediction using this objective variable is even more precise when 3 levels of SpO_2 (> 95%, ≤ 95%, and ≤ 90%) are considered.[2] In other clinical settings, a low SpO_2 is emerging as a good predictor of outcome.[33, 34] The incidence of $SpO_2 \leq 95\%$ in our surgical cohort (18.8%) was much higher than the incidence of 6.3% in a recent population-based study.[35] We interpret this as a sign that a surgical

population will tend towards impaired cardio-respiratory function. Exclusion of SpO_2 from the score when this measurement is not available (for example, in clinical settings where phone screening is used), reduces its performance. Calibration suffers in particular, meaning that the model without SpO_2, might not accurately assess level of risk. (See supplementary Table 2.) We therefore think that routine measurement of preoperative SpO_2 should be encouraged and that it will probably prove to be a robust predictor of poor postoperative outcome.

Preoperative heart failure is a well recognised risk factor for the development of PPCs.[1, 5, 22] In our study, we analysed 3 levels of heart failure according to the NYHA classification, finding that PRF risk increased with severity. We also identified chronic liver disease as a predictor of PRF. Chronic liver disease has been linked to a poor postoperative prognosis overall.[36] One retrospective study found an association between liver disease and unanticipated early postoperative tracheal intubation after nonemergent noncardiac surgery,[5] and a retrospective study identified an 8% rate of ventilatory dependence (postoperative mechanical ventilation >24 hours or unplanned intubation) and a similar rate for pneumonia in 733 cirrhotic patients undergoing any surgical procedure.[37] However, chronic liver disease encompasses a wide spectrum of disorders ranging from fatty liver disease to cirrhosis. No study has sought to define a relationship between the different kinds of liver disease and PRF or other PPCs to date. We did not record different types of liver disease in our study, but the strong association we found between this factor and PRF suggests that more accurate records should be used in future studies.

The 3 remaining independent risk factors were associated with surgical procedure. In most previous studies surgical incision, duration of surgery, and emergency status have been proposed as predictors of PPCs.[22] However, in the PRF score we present, we further distinguished open and closed surgery because closed surgery has been associated with less postoperative pneumonia, PRF and mortality,[38] consistent with our finding that closed abdominal surgery approximately halved the risk for PRF and closed thoracic surgery reduced risk 4-fold.

Thus, although the identified risk factors differ slightly from study to study, we see commonalities. Patient-associated risk factors, which depend fundamentally on comorbidity, and procedure-associated risk factors are very similar across the studies. High risk and emergent surgery were identified as risk factors in most of the studies. [1, 3, 4, 7]

A strength of our study is that all variables were chosen and defined a priori and cases were identified prospectively by daily searches of records. Moreover, we included patients undergoing a broad spectrum of surgeries rather than limiting the study to an specific patient population or procedure.[39] This approach sought to enhance the reliability of the findings so that they would be generalisable to the real world of anaesthetics and surgery.

A limitation of this study is that postoperative follow-up ended at hospital discharge. Second, the cohort was recruited by volunteer hospitals that did not cover the entire territory of Europe. Third, possible intraoperative events that might be related to PRF, such as respiratory complications, blood loss or ventilatory management, were not taken into account. Fourth,

the present study reports internal validation of the score; external validation remains to be performed.

Identifying patients at high risk for developing PRF is of great value in clinical making-decision about perioperative measures to be applied. Among the measures that have been shown to reduce the incidence of PRF, we mention preoperative optimisation of some health conditions such as smoking and alcohol cessation,[40, 41] intraoperative ventilatory management,[42-44] and postoperative analgesia and physiotherapy.[45, 46] Although strategies to reduce PRF risk have also been shown to reduce health costs,[47-50] randomised trials to test the efficacy of preventive measures are still lacking. The PERISCOPE-PRF score developed in this study can be useful for classifying patients systematically in such trials.

In conclusion, PRF is a frequent complication and is associated with a poor prognosis, but the PERISCOPE-PRF score is likely to help identify surgical patients at risk so that stricter measures to prevent this life-threatening complication can be considered.

Acknowledgements

The PERISCOPE study was funded and supported through the ESA's Clinical Trials Network. The off-site data manager who checked entries for completeness was an ESA staff member. The ESA also supported organisational meetings, communication between centres, and manuscript editing for English language expression. The authors thank Brigitte Leva, of the ESA, for her assistance as data manager, and Mary Ellen Kerans, for

manuscript editing and advice on the English usage in some versions of the manuscript.

All authors declare no conflict of interest.

Figure legends

Figure 1. Recruitment flowchart.

Figure 2. Plot of survival predicted by the risk score against overall (actuarial) survival after development of mild, moderate, or severe postoperative respiratory failure (PRF).

Figure 3. The risk model's performance: A, Receiver operating characteristics curve (to show discrimination); B, Agreement between observed frequency and predicted probability at 3 levels of risk (to assess calibration). Triangles represent the values for risk groups (patients whose scores reflected low, intermediate, or high risk). AUC = area under curve (*c*-statistic); H-L χ^2 = Hosmer-Lemeshow chi-square goodness-of-fit test.

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* Site leader.

PERISCOPE = Prospective Evaluation of a RIsk Score for postoperative pulmonary COmPlications in Europe

table 1

Table 1. **Demographic and Clinical Characteristics***

Total No. (%) of patients	5384 (100)
Male sex, n (%)	2733 (50.8)
Age, median (IQR), y	58.9 (26.1)
Smoking status, n (%)	
Never smoker	2833 (52.6)
Former smoker	1309 (24.3)
Current smoker	1242 (23.1)
Preoperative SpO_2, median (IQR), %	97 (3)
Body mass index, median (IQR), kg/m^2	26.1 (5.9)
COPD, n (%)	538 (10.0)
Respiratory infection in the last month, n (%)	298 (5.5)
ASA physical status, n (%)	
1	1204 (22.4)
2	2738 (50.8)
3	1336 (24.8)
4	106 (2.0)
Emergency surgery, n (%)	609 (11.3)
Anaesthesia, n (%)	
General and combined †	4125 (76.6)

Neuraxial/Regional	1259 (23.4)
Surgical specialty, n (%)	
General and digestive	1427 (26.5)
Orthopaedic	1064 (19.8)
Urology	702 (13.0)
Gynaecology	452 (8.4)
Neurosurgery	333 (6.2)
ENT	322 (6.0)
Vascular	211 (3.9)
Cardiac	167 (3.1)
Breast	161 (3.0)
Thoracic	145 (2.7)
Other	400 (7.4)
Duration of surgery, median (IQR), h	1.3 (1.4)
~~Postoperative~~ Preoperative length of stay, median (IQR), d	1 (1)
Postoperative ICU admission, n (%)	499 (9.3)
ICU length of stay, median (IQR), h	24 (55)
Postoperative hospital length of stay, median (IQR), d	4 (5)
In-hospital mortality, n (%)	46 (0.9)

ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; ENT = ears nose and throat; ICU = intensive care unit; IQR = interquartile range; SpO_2 = oxyhaemoglobin saturation by pulse oximetry breathing air in supine position.
* Data are number of patients unless otherwise indicated.

† This category included general anaesthesia alone and general anaesthesia combined with regional blockade.

table 2

Table 2. **Bivariate Analysis for Independent Predictors of Postoperative Respiratory Failure**

	No. of Patients			Patients with PRF		
	Total	% over total No of patients	Missing	~~With PRF,~~ n	%	*P* Value
Total	5384	100		224	4.2	
Variables entered into the multiple regression model						
Gender			0			0.009
Female	2651	49.2		91	3.4	
Male	2733	50.8		133	4.9	
Age, y			0			<0.001
≤ 50	1893	35.2		40	2.1	
50 to 70	2173	40.4		101	4.6	
>70	1318	24.4		83	6.3	
Functional status			0			<0.001
Independent	4823	89.6		171	3.5	
Partially/totally dependent	562	10.4		53	9.4	
~~Postoperative~~ Preoperative length of stay, d			0			< 0.001
< 2	4179	77.6		144	3.4	
≥ 2	1205	22.4		80	6.6	
SpO_2, %			128			<0.001
≥96	4267	79.3		124	2.9	
91 – 95	923	17.1		84	9.1	
≤ 90	66	1.2		12	18.2	
Preoperative respiratory symptoms (at least 1)			0			<0.001
No	4003	74.3		94	2.3	
Yes	1381	25.7		130	9.4	
Lifetime smoking exposure, pack-years			88			0.005
0	2833	52.6		95	3.4	

1 – 40	2120	39.4		107	5.0	
> 40	343	6.4		19	5.5	
History of congestive heart failure			0			< 0.001
No	4543	84.4		129	2.8	
NYHA I	330	6.1		20	6.1	
NYHA II – IV	511	9.5		75	17.7	
Chronic kidney disease*			0			< 0.001
No	5118	95.1		199	3.9	
Yes	266	4.9		25	9.4	
Anaemia†			167			< 0.001
No	4065	75.5		145	3.6	
Yes	1152	21.4		78	6.8	
Liver disease			0			< 0.001
No	5075	94.3		195	3.8	
Yes	309	5.7		29	9.4	
Type of surgery			0			<0.001
Scheduled	4775	88.7		170	3.6	
Emergency	609	11.3		54	8.9	
Duration of surgery, h			0			<0.001
< 2	3876	72.0		108	2.8	
2 — 3	791	14.7		43	5.4	
> 3	717	13.3		73	10.2	
Surgical incision			0			<0.001
Peripheral and other	3917	72.8		106	2.7	
Closed intrathoracic/upper abdominal	685	12.7		27	3.9	
Upper abdominal open	528	9.8		43	8.1	
Intrathoracic open	254	4.7		48	18.5	
Significant variables not entered into the model (*P* value > 0.05 or high colinearity, i.e., correlation coefficient > 0.25)						
ASA physical status			0			< 0.001

1	1204	22.4		10	0.8	
2	2738	50.8		65	2.4	
3	1336	24.8		131	9.8	
4	106	2.0		18	17.0	
BMI, kg/m^2			0			0.496
< 35	5057	93.9		210	4.2	
≥ 35	327	6.1		14	4.3	
Smoking status			0			0.007
Never smoker	2833	52.6		95	3.4	
Current smoker	1242	23.1		62	5.0	
Former smoker	1309	24.3		67	5.1	
COPD			0			<0.001
No	4864	90.0		165	3.4	
Yes	538	10.0		59	11	
Cough test‡			408			<0.001
Negative	3941	73.2		119	3.0	
Positive	1035	19.2		73	7.1	
Respiratory infection last month			2			0.176
No	5084	94.5		208	4.1	
Yes	298	5.5		16	5.4	
History of coronary artery disease			0			< 0.001
No	4707	87.4		145	3.1	
Yes	677	12.6		79	11.7	
History of cerebrovascular disease			0			0.001
No	4706	87.4		181	3.8	
Yes	678	12.6		43	6.3	
Hypertension			0			< 0.001
No	3096	57.5		73	2.4	
Yes	2288	42.5		151	6.6	
Anaesthetic technique			0			0.025

~~Regional~~ Neuraxial/Regional	1259	23.4		40	3.2	
General and combined ††	4125	76.6		184	4.5	
Fluid therapy, ml/kg/h			0			0.759
≤ 6	764	14.2		28	3.7	
> 6 - 9	1017	18.9		40	3.9	
> 9 - 13	1275	23.7		52	4.1	
≥ 13	2328	43.2		104	4.5	
Intraoperative colloids			0			<0.001
No	4075	75.7		89	2.2	
Yes	1309	24.3		135	10.3	
Intraoperative RBC transfusion			0			<0.001
No	5076	94.3		171	3.4	
Yes	308	5.7		53	17.2	

ASA = American Society of Anesthesiologists physical status classification; BMI = Body Mass Index; COPD = chronic obstructive pulmonary disease; PRF = postoperative respiratory failure; RBC = red blood cells; SpO_2 = peripheral arterial oxygen saturation breathing room air in supine position measured by pulse oximetry

*Renal failure, defined as serum creatinine >2.0 mg/dL.

† In females, < 12 g/dL; in males, < 13 g/dL.

‡ In the cough test, the patient is asked to take a deep breath and cough once. A positive test is defined by repeated coughing after the first cough.

†† This category included general anaesthesia alone and general anaesthesia combined with regional blockade.

table 3

Table 3. **Independent Predictors of Risk for PRF Identified by Logistic Regression** *

	Bivariate Analysis OR (95% CI) ~~N~~ n = 5384	Multivariate Analysis OR (95% CI) n = 5256	β Coefficients	Corrected β Coefficients† β (95% CI)	Risk Score‡
Patient health related factors					
Preoperative SpO_2, %					
≥96	1	1			
91 – 95	3.4 (2.5 – 4.5)	2.0 (1.5 – 2.8)	0.704	0.696 (0.380 – 1.007)	7
90	7.4 (3.9 – 14.2)	2.7 (1.3 – 2.9)	0.982	0.982 (0.204 – 1.691)	10
Respiratory symptoms (at least 1)	4.3 (3.3 – 5.7)	2.7 (1.9 – 3.6)	0.984	0.983 (0.676 – 1.291)	10
History of congestive heart failure					
No	1	1			
NYHA I	2.2 (1.4 – 3.6)	1.3 (0.8 – 2.2)	0.270	0.273 (–0.281 – 0.775)	3
NYHA ≥ II	5.9 (4.4 – 7.9)	2.2 (1.6 – 3.2)	0.806	0.802 (0.442 – 1.154)	8

History of chronic liver disease	2.6 (1.7 – 3.9)	2.1 (1.3 – 3.2)	0.729	0.730 (0.270 – 1.160)	7
Procedures related factors					
Emergency procedure	2.6 (1.9 – 3.6)	3.1 (2.2 – 4.5)	1.144	1.150 (0.777 – 1.511)	12
Surgical incision					
Peripheral	1	1			
Closed intrathoracic / closed upper abdominal	1.5 (1.0 – 2.3)	1.3 (0.9 – 2.1)	0.291	0.303 (–0.171 – 0.743)	3
Open upper abdominal	3.2 (2.2 – 4.6)	1.9 (1.3 – 2.9)	0.667	0.662 (0.247 – 1.062)	7
Intrathoracic open	8.4 (5.8 – 12.1)	3.3 (2.1 – 5.3)	1.195	1.187 (0.715 – 1.649)	12
Duration of surgery, h					
≤ 2	1	1			
>2 to 3	2.0 (1.4 – 2.9)	1.6 (1.1 – 2.4)	0.453	0.456 (0.046 – 0.849)	5
> 3	3.9 (2.9 – 5.4)	2.7 (1.8 – 3.9)	0.983	0.991 (0.601 – 1.372)	10

CI = confidence interval; OR = odds ratio; NYHA = New York Heart Association scale; SpO_2 = oxyhaemoglobin saturation by pulse oximetry breathing air in supine position. Because of a missing value for some variables, 128 patients were excluded.

* Logistic regression model (*c*-statistic = 0.82; Hosmer-Lemeshow chi-square test = 7.080; *P* = 0.253).

† After bootstrap resampling (1000 bootstrap subsamples).

‡ The simplified risk score was the sum of each corrected β coefficient multiplied by 10 and then rounded.

table 4

Table 4. **Sensitivity, Specificity, and Positive and Negative Likelihood Ratios for the Ability of the Simplified Risk Score to Predict Intermediate (≥ 12 Points) and High Risk (≥ 23 Points)**

	Cutoff ≥ 12*	Cutoff ≥ 23*
Sensitivity	84.6% (79.1% – 89.1%)	55.9% (49.1% – 62.6%)
Specificity	63.3% (61.9% – 64.6%)	89.4% (88.6% – 90.3%)
Positive likelihood ratio	2.3 (2.2 – 2.5)	5.3 (4.6 – 6.1)
Negative likelihood ratio	0.2 (0.18 – 0.33)	0.5 (0.4 – 0.6)
Positive predictive value	9.1 (7.9 – 10.5)	18.8 (15.9 – 21.9)
Negative predictive value	98.9 (98.5 – 99.3)	97.9 (97.4 – 98.3)

* Data between parentheses are 95% confidence intervals.

Figure 1

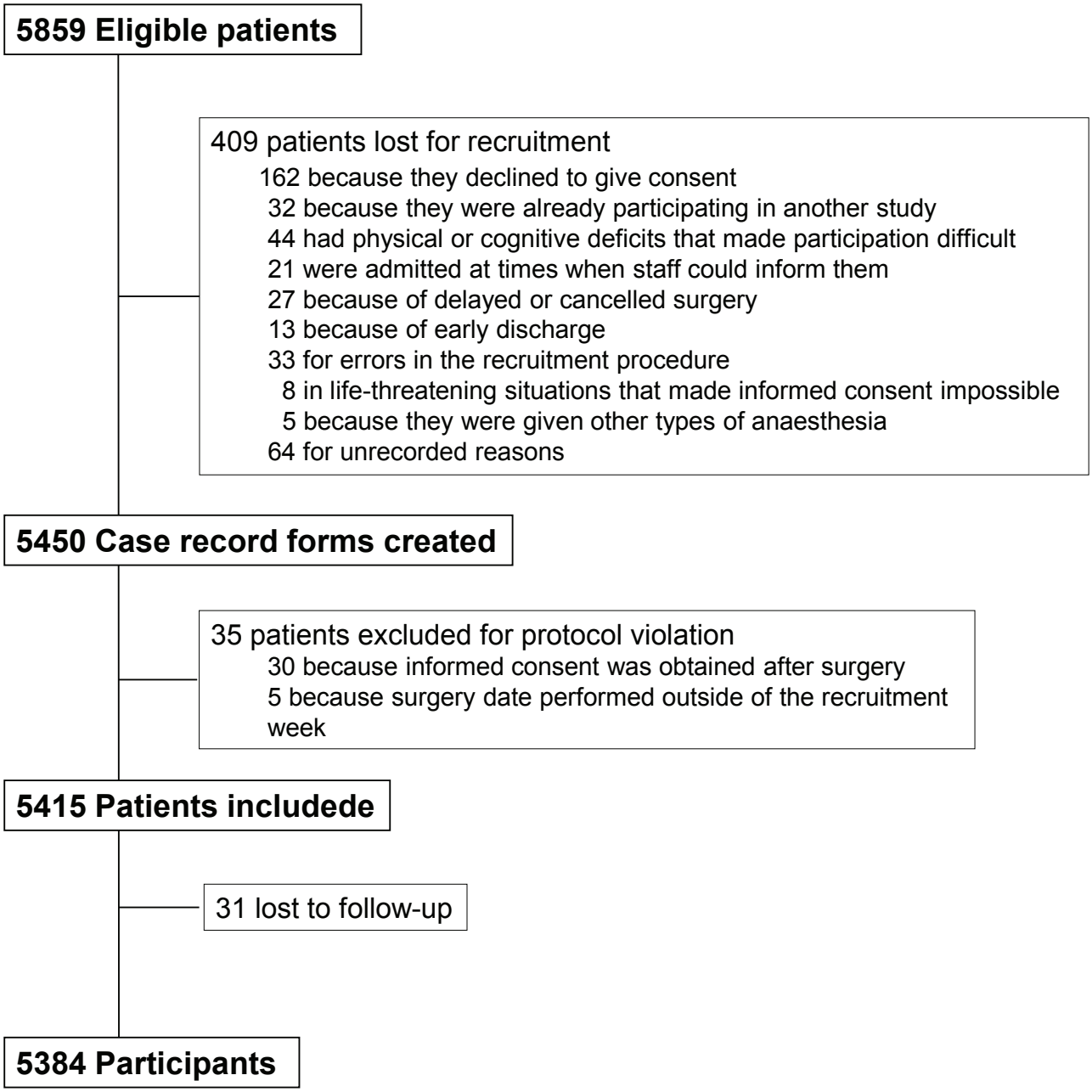
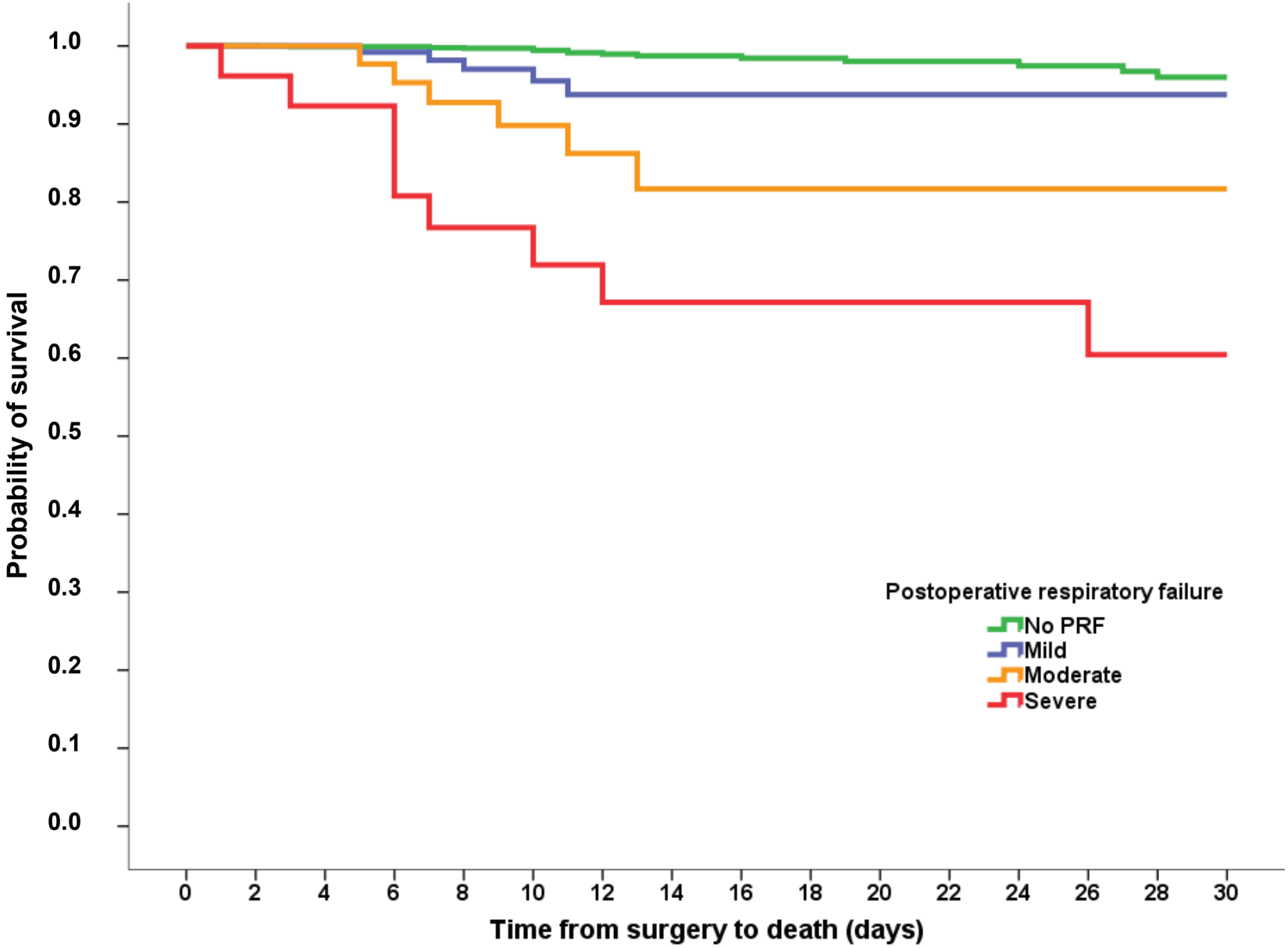
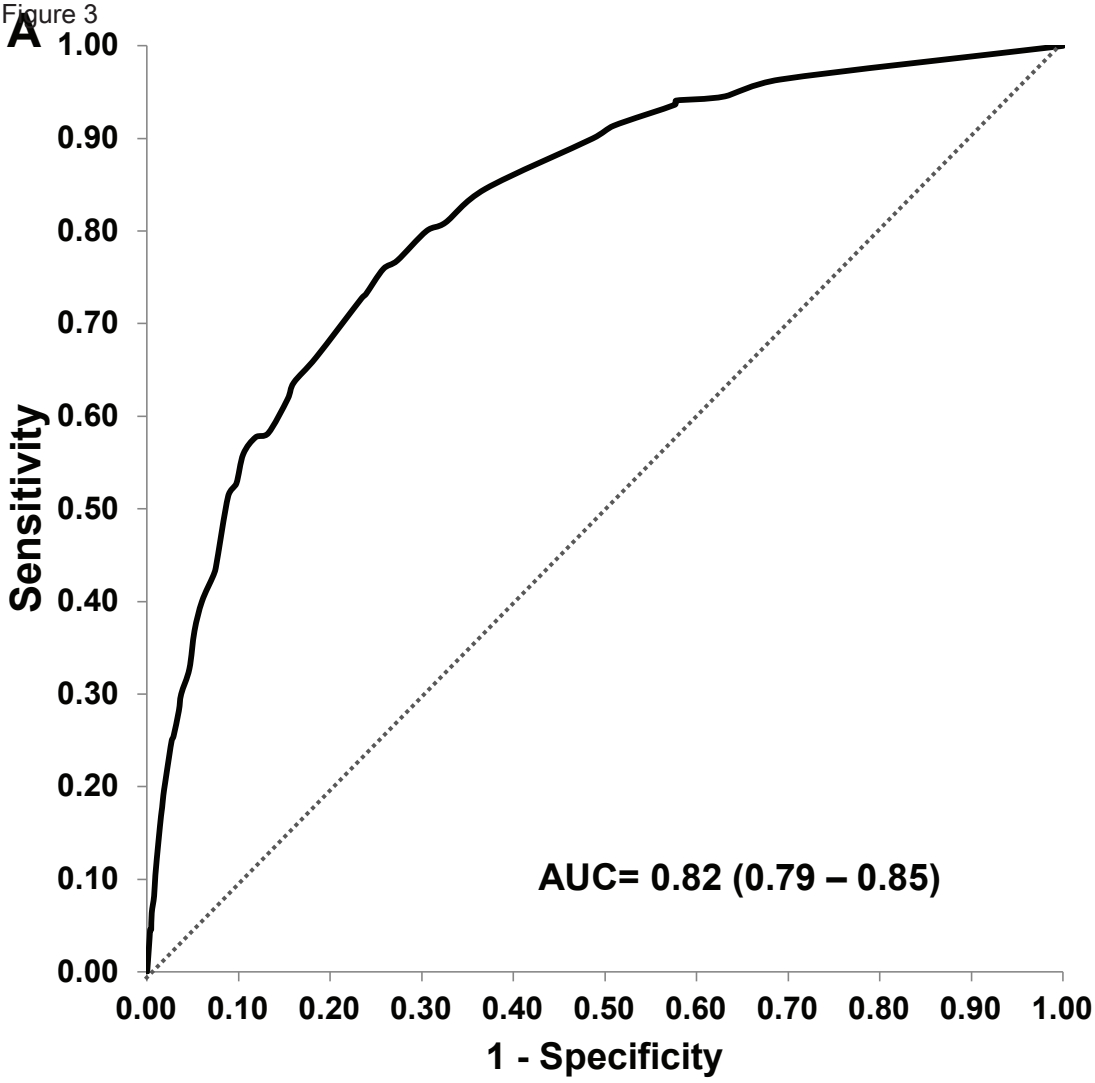

5859 Eligible patients
409 patients lost for recruitment
162 because they declined to give consent
32 because they were already participating in another study
44 had physical or cognitive deficits that made participation difficult
21 were admitted at times when staff could inform them
27 because of delayed or cancelled surgery
13 because of early discharge
33 for errors in the recruitment procedure
8 in life-threatening situations that made informed consent impossible
5 because they were given other types of anaesthesia
64 for unrecorded reasons
5450 Case record forms created
35 patients excluded for protocol violation
30 because informed consent was obtained after surgery
5 because surgery date performed outside of the recruitment week
5415 Patients includede
31 lost to follow-up
5384 Participants

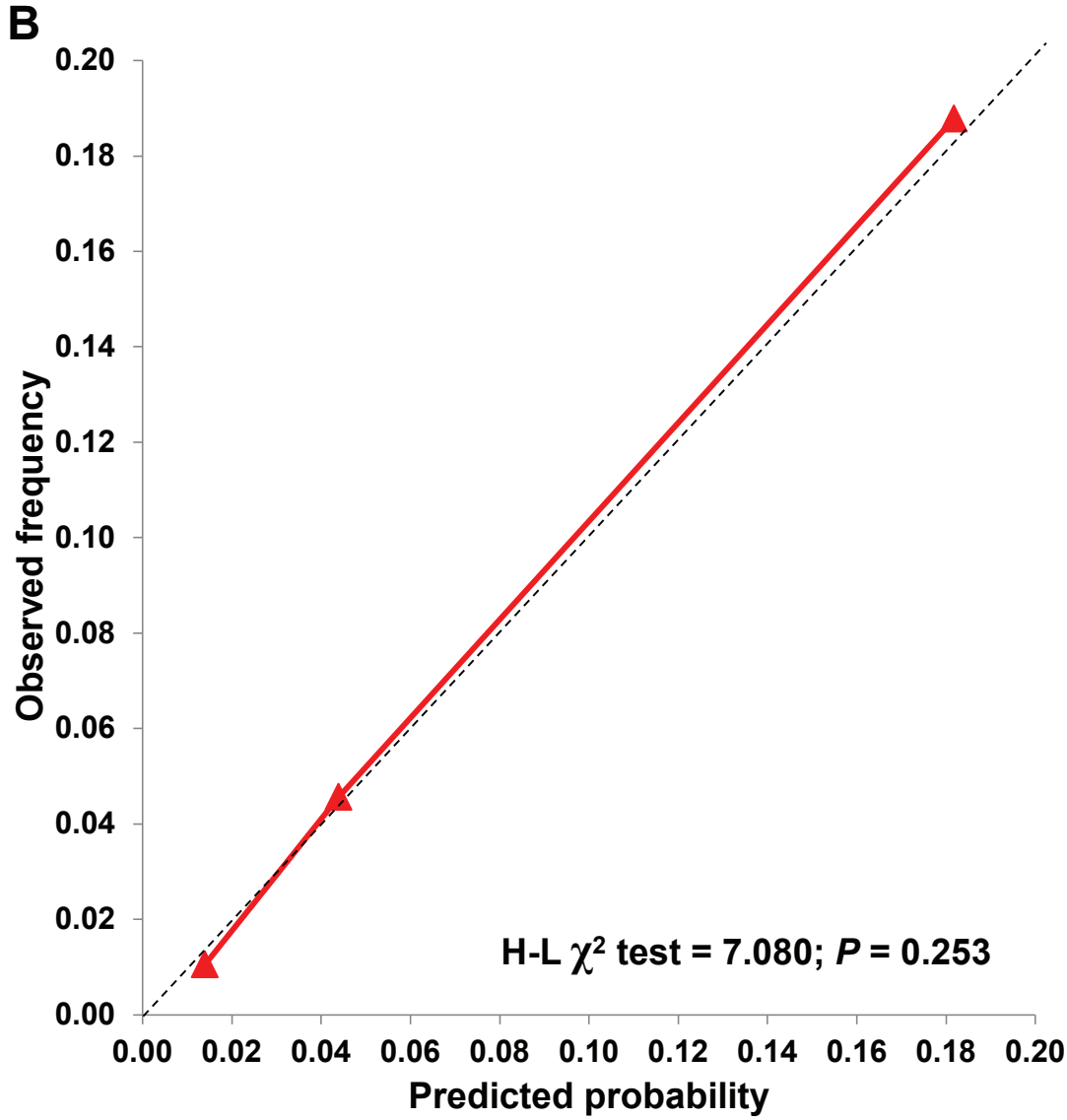
Figure 2



No. of patients																
No PRF	5160	4179	2648	1762	1081	694	517	401	299	248	217	182	160	144	126	110
Mild	155	150	128	105	80	59	43	31	21	17	16	14	14	14	14	14
Moderate	43	43	43	39	32	26	20	14	9	6	6	5	5	5	5	5
Severe	26	25	24	21	18	15	14	13	11	11	11	11	10	9	9	9

Figure 3


A
Sensitivity
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
AUC= 0.82 (0.79 – 0.85)
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
1 - Specificity


B
Observed frequency
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
H-L χ² test = 7.080; P = 0.253
0.00 0.02 0.04 0.06 0.08 0.10 0.12 0.14 0.16 0.18 0.20
Predicted probability