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Digital Health

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: NIHR Global Health Research Unit on Global Surgery, STARSurg Collaborative. A prognostic model for use before elective surgery to estimate the risk of postoperative pulmonary complications (GSU-Pulmonary Score): a development and validation study in three international cohorts. *Lancet Digit Health* 2024; **6**: e507–19.

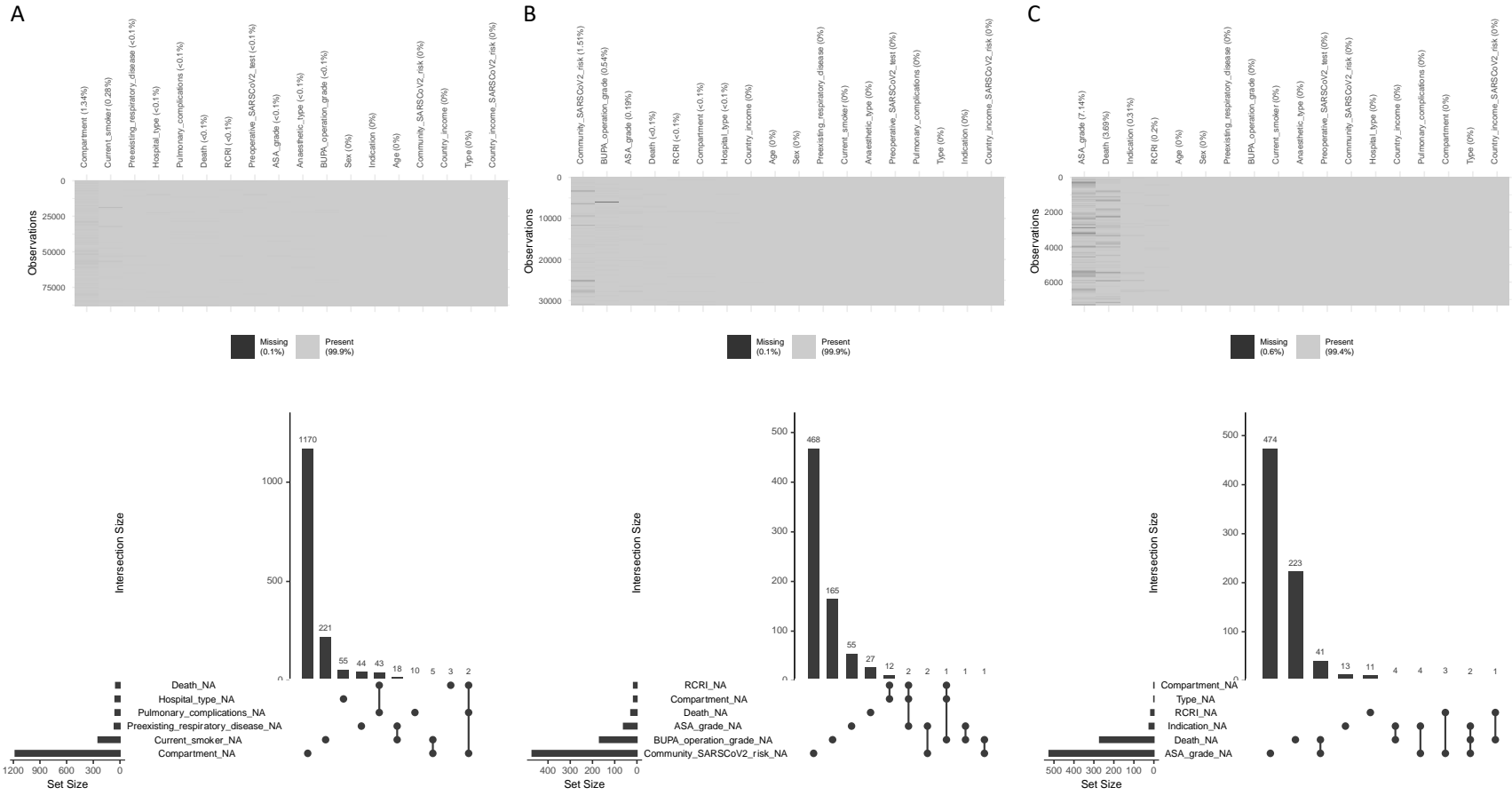
Risk of pulmonary complications in adults undergoing elective surgery: Development and validation of a prognostic model to support safe global recovery of elective surgery (GSU-Pulmonary Score)

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Supplementary figure 1. Summary of missing values in (A) derivation: whole set, (B) validation (CovidSurg-Cancer), (C) validation (RECON)



Supplementary figure 2. Comparison of LASSO and XGBoost techniques during model selection

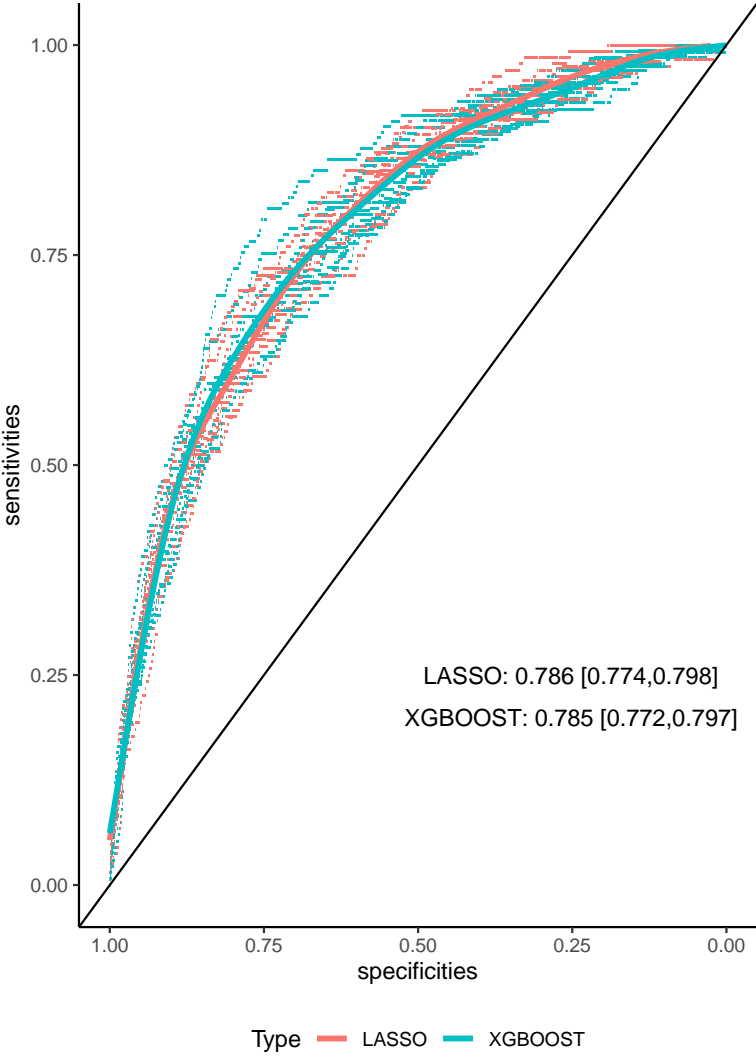
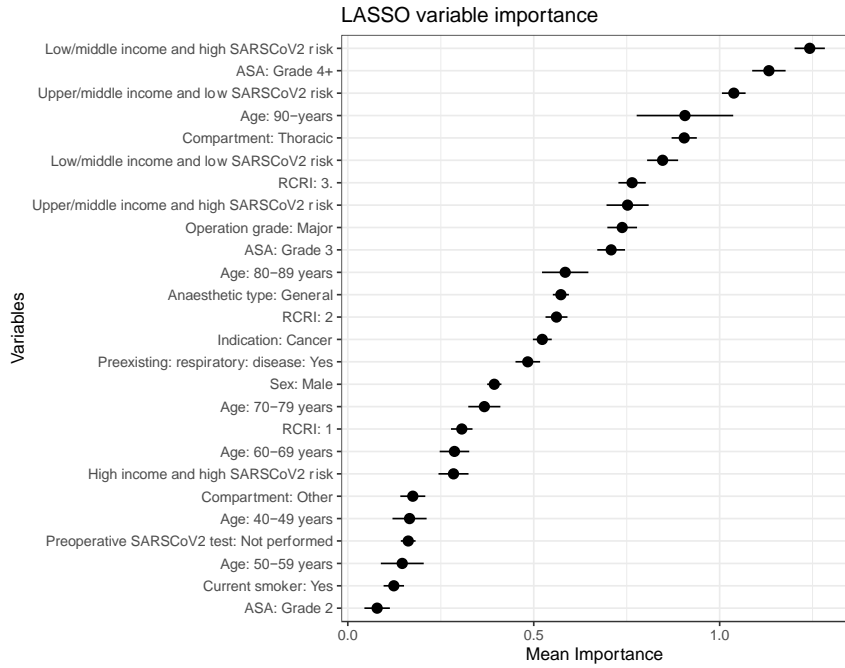
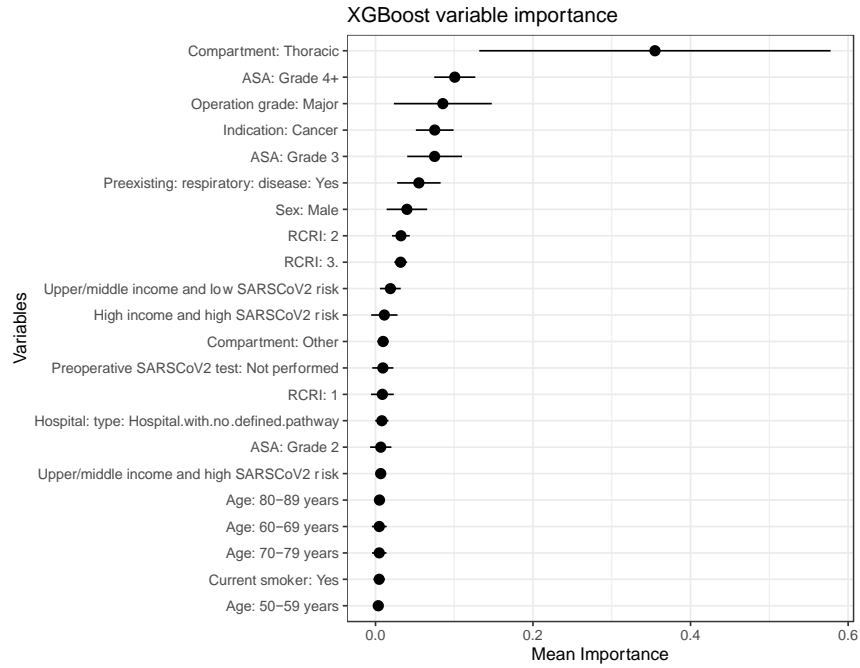
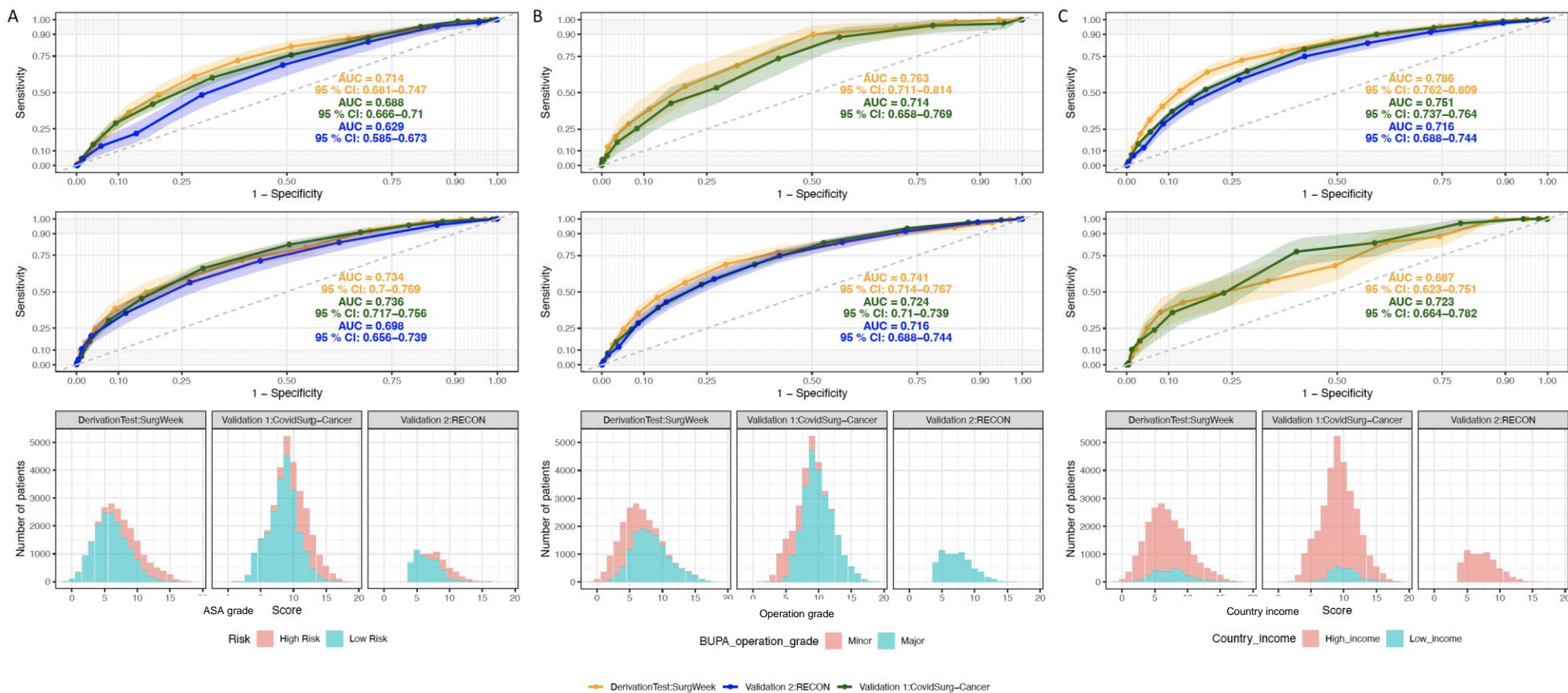


Figure displays bootstrapped resamplings for both XGBoost and LASSO models, and the overall AUROCs for each model type in bold.

Supplementary figure 3. Variable importance measures in LASSO and XGBoost

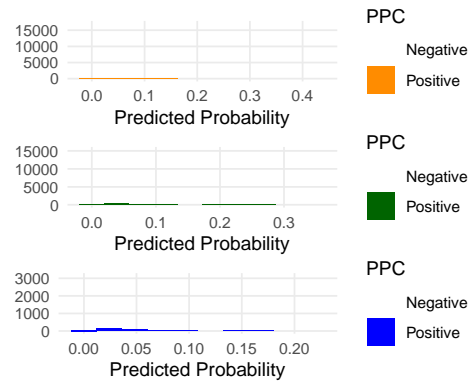
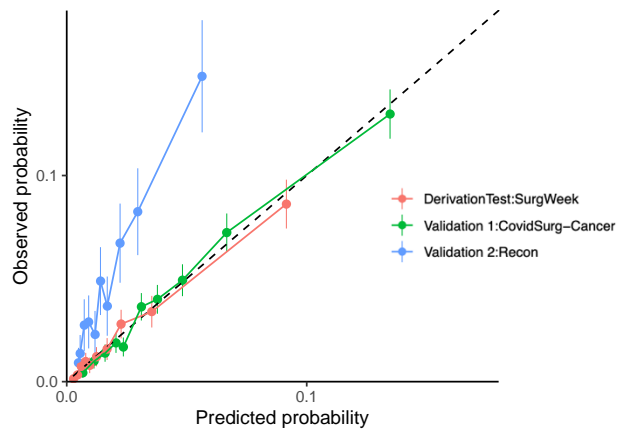
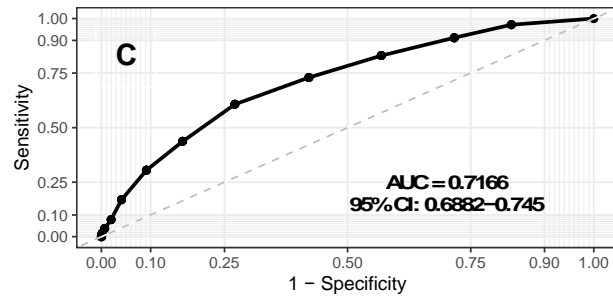
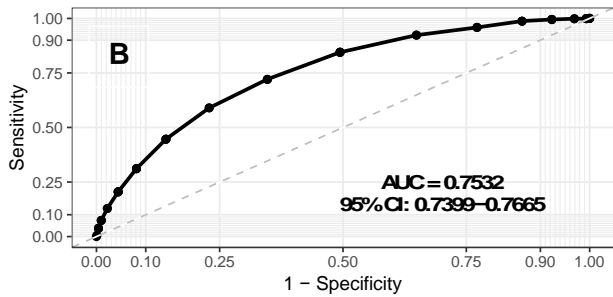
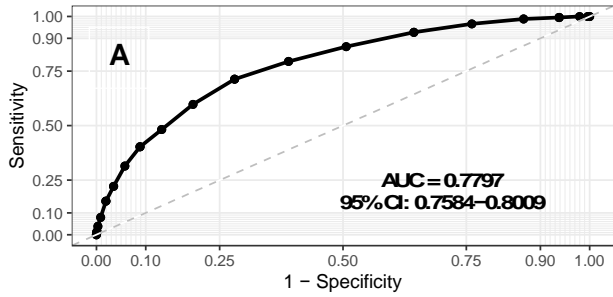


Supplementary figure 4. Performance of GSU-Pulmonary Score across key subgroups in derivation: testing set, validation (CovidSurg-Cancer), and validation (RECON) datasets

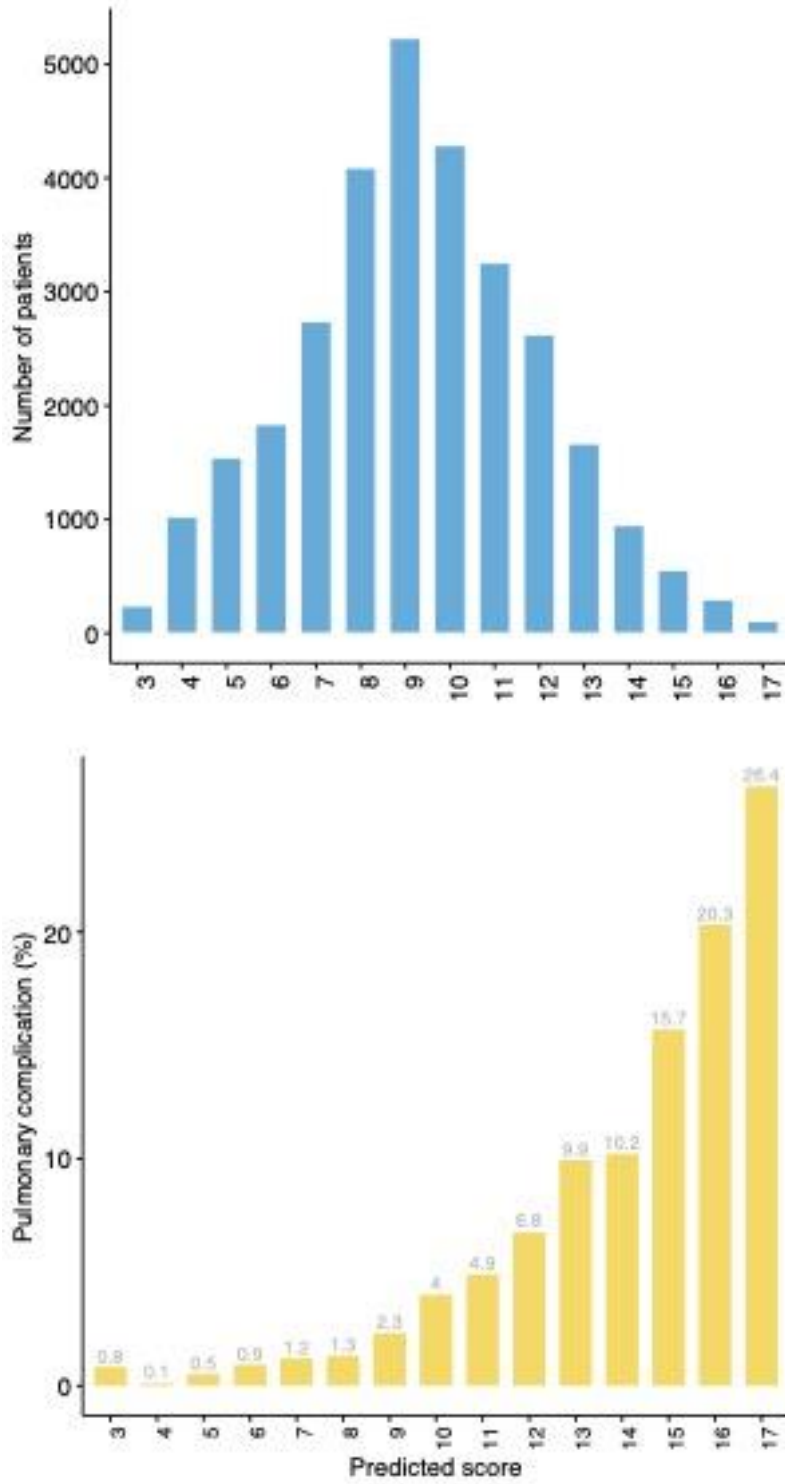


Subgroup analyses displayed for derivation and validation datasets (top and middle), and number of patients across each point of the GSU-Pulmonary Score range (bottom). Subgroup analyses presented include by (A) American Society of Anaesthesiologists physical classification system (ASA) grade: high risk (ASA 3-5) versus low risk (ASA 1-2), (B) BUPA operation grade: minor versus major, and (C) Country income group: High-income versus Low-middle income.

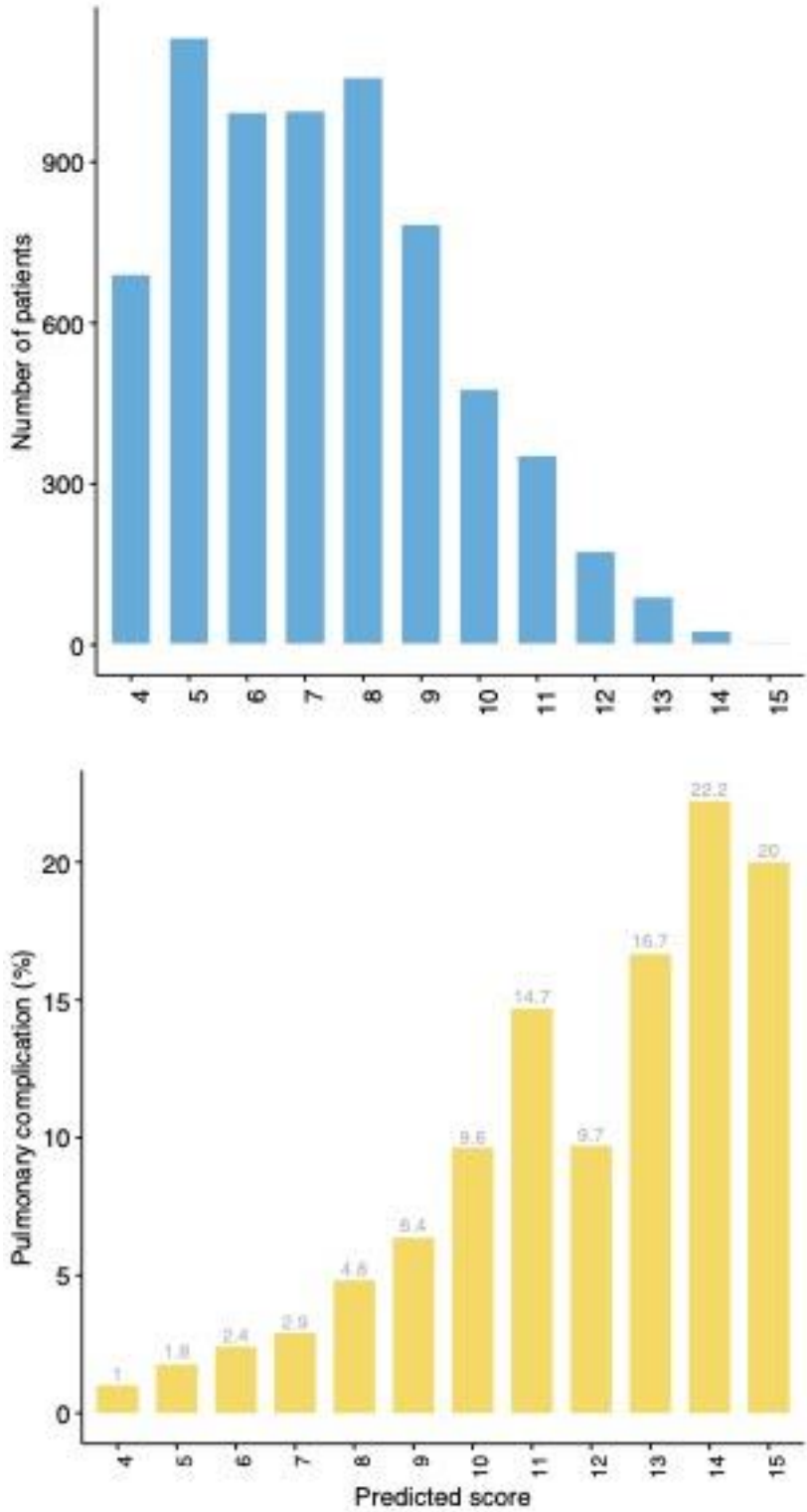
Supplementary figure 5. Sensitivity analysis to account for death as a competing risk in (A) derivation: testing set, (B) validation (CovidSurg-Cancer), (C) validation (RECON) datasets



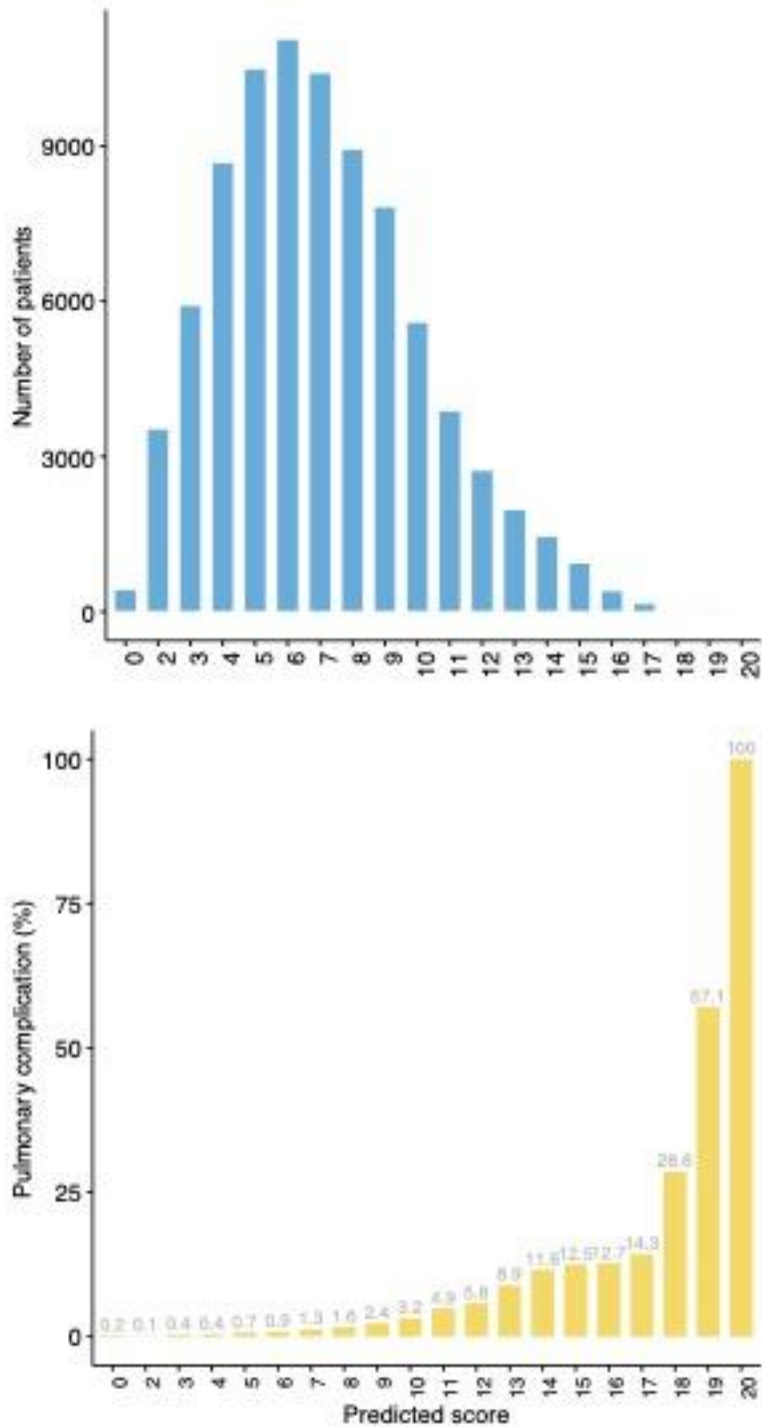
Supplementary figure 6A. Summary of GSU-Pulmonary Score versus predicted pulmonary complication rates in the validation (CovidSurg-Cancer) dataset



Supplementary figure 6B. Summary of GSU-Pulmonary Score versus predicted pulmonary complication rates in the validation (RECON) dataset

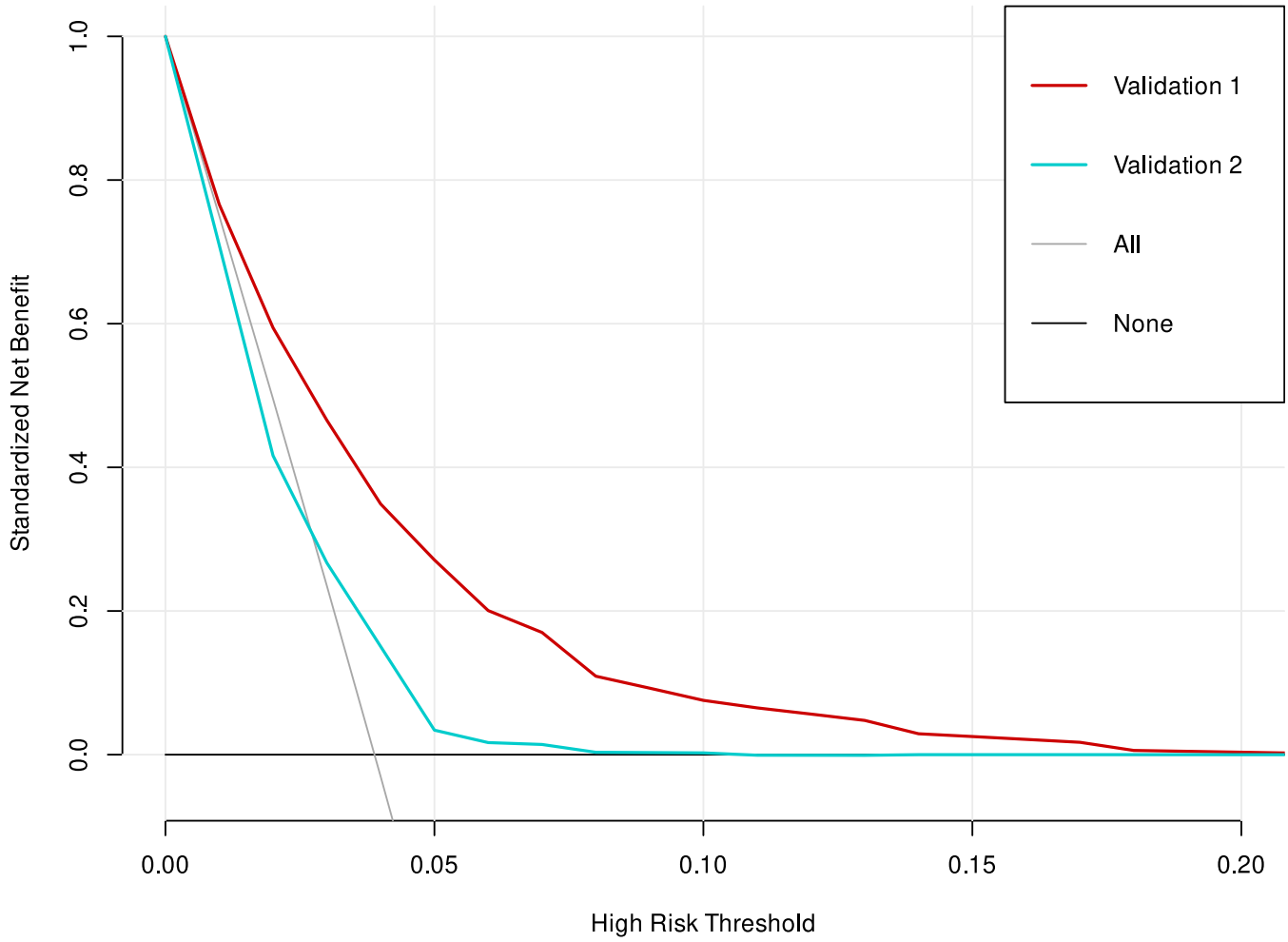


Supplementary figure 7. Summary of GSU-Pulmonary Score versus predicted pulmonary complication rates in the derivation: whole dataset



Summaries of the validation (CovidSurg-Cancer) and validation (RECON) datasets is presented in Supplementary figure 4A and 4B

Supplementary figure 8. Decision curve analysis for GlobalSurg Pulmonary Score



Lines are shown for standardised net benefit at different risk thresholds of treating no patients (black line) and treating all patients (grey line)

Supplementary table 1. Summary of missing data

Features	Derivation GlobalSurg/ CovidSurg-Week N= 87,806	Validation CovidSurg-Cancer N=30,978	Validation RECON N=6,818
Patient factors			
Age	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sex	3 (0.0%)	0 (0.0%)	0 (0.0%)
ASA grade	35 (0.0%)	60 (0.2%)	524 (7.1%)
RCRI	47 (0.1%)	15 (0.1%)	15 (0.2%)
Pre-existing respiratory disease	63 (0.1%)	0 (0.0%)	0 (0.0%)
Current smoker	245 (0.3%)	0 (0.0%)	0 (0.0%)
Disease factors			
Compartment	1178 (1.3%)	15 (0.1%)	0 (0.0%)
Indication	3 (0.0%)	0 (0.0%)	23 (0.3%)
Preoperative SARS-CoV-2 test	42 (0.1%)	0 (0.0%)	0 (0.0%)
Operation factors			
Anaesthetic type	32 (0.0%)	0 (0.0%)	0 (0.0%)
Operation grade	22 (0.0%)	168 (0.5%)	0 (0.0%)
Location factors			
Hospital type	55 (0.1%)	5 (0.0%)	0 (0.0%)
Country income	0 (0.0%)	1 (0.0%)	0 (0.0%)
Community SARS-CoV-2 risk	0 (0.0%)	471 (1.5%)	0 (0.0%)
Outcome measures			
Pulmonary complications	55 (0.1%)	0 (0.0%)	0 (0.0%)
Death	3 (0.0%)	24 (0.1%)	223 (3.7%)

Supplementary table 2. GSU-Pulmonary Score cut-off point scores and prognostic test accuracy measures (derivation: whole dataset)

Cut-off point score	Patients N (%)	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Pulmonary complications (%)
'Rule out' pulmonary complications										
≤5	30689 (35.59)	1644	30068	53898	136	92.36	35.81	2.96	99.55	0.44
≤7	52181 (60.51)	1415	51331	32635	365	79.49	61.13	4.16	99.29	0.7
≤9	68969 (79.98)	1084	67788	16178	696	60.9	80.73	6.28	98.98	1.01
≤11	78468 (91)	716	76919	7047	1064	40.22	91.61	9.22	98.64	1.36
≤13	83191 (96.47)	381	81307	2659	1399	21.4	96.83	12.53	98.31	1.68
≤15	85604 (99.27)	92	83431	535	1688	5.17	99.36	14.67	98.02	1.97
≤17	86188 (99.95)	15	83938	28	1765	0.84	99.97	34.88	97.94	2.05
≤19	86230 (100)	1	83966	0	1779	0.06	100	100	97.93	2.06
'Rule in' pulmonary complications										
≥5	66047 (76.59)	1720	19639	64327	60	96.63	23.39	2.6	99.7	2.6
≥7	44467 (51.57)	1549	41048	42918	231	87.02	48.89	3.48	99.44	3.48
≥9	25097 (29.1)	1269	60138	23828	511	71.29	71.62	5.06	99.16	5.06
≥11	11654 (13.51)	905	73217	10749	875	50.84	87.2	7.77	98.82	7.77
≥13	5022 (5.82)	557	79501	4465	1223	31.29	94.68	11.09	98.48	11.09
≥15	1577 (1.83)	211	82600	1366	1569	11.85	98.37	13.38	98.14	13.38
≥17	211 (0.24)	39	83794	172	1741	2.19	99.8	18.48	97.96	18.48
≥19	8 (0.01)	5	83963	3	1775	0.28	100	62.5	97.93	62.5

Prognostic test accuracy in the validation (CovidSurg-Cancer) and validation (RECON) datasets is presented in Supplementary table 1 and 2. TP=True positive. TN=True negative. FP=False positive. FN=False negative. PPV=Positive predictive value. NPV=Negative predictive value.

Supplementary table 3. GSU-Pulmonary Score cut-off point scores and prognostic test accuracy measures in the validation (CovidSurg-Cancer) dataset

Cut-off point score	Patients N= (%)	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Pulmonary complications (%)
'Rule out' pulmonary complications										
≤5	2830 (9.28)	1174	2819	26487	11	99.07	9.62	4.24	99.61	0.39
≤7	7407 (24.29)	1124	7346	21960	61	94.85	25.07	4.87	99.18	0.82
≤9	16728 (54.86)	948	16491	12815	237	80	56.27	6.89	98.58	1.42
≤11	24272 (79.6)	616	23703	5603	569	51.98	80.88	9.91	97.66	2.34
≤13	28565 (93.68)	273	27653	1653	912	23.04	94.36	14.17	96.81	3.19
≤15	30068 (98.61)	89	28972	334	1096	7.51	98.86	21.04	96.35	3.65
≤17	30474 (99.94)	0	29289	17	1185	0	99.94	0	96.11	3.89
'Rule in pulmonary complications										
≥5	29208 (95.79)	1182	1281	28025	3	99.75	4.37	4.05	99.77	4.05
≥7	25825 (84.69)	1157	4639	24667	28	97.64	15.83	4.48	99.4	4.48
≥9	18993 (62.29)	1070	11384	17922	115	90.3	38.85	5.63	99	5.63
≥11	9476 (31.08)	776	20607	8699	409	65.49	70.32	8.19	98.05	8.19
≥13	3596 (11.79)	439	26150	3156	746	37.05	89.23	12.21	97.23	12.21
≥15	978 (3.21)	176	28505	801	1009	14.85	97.27	18.01	96.58	18
≥17	124 (0.41)	28	29211	95	1157	2.36	99.68	22.76	96.19	22.58

TP=True positive. TN=True negative. FP=False positive. FN=False negative. PPV=Positive predictive value. NPV=Negative predictive value.

Supplementary table 4. GSU-Pulmonary Score cut-off point scores and prognostic test accuracy measures in the validation (RECON) dataset

Cut-off point score	Patients N= (%)	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Pulmonary complications (%)
'Rule out' pulmonary complications										
≤5	1825 (26.88)	291	1798	4671	27	91.51	27.79	5.86	98.52	1.48
≤7	3815 (56.19)	238	3735	2734	80	74.84	57.74	8.01	97.9	2.1
≤9	5659 (83.36)	137	5478	991	181	43.08	84.68	12.15	96.8	3.2
≤11	6490 (95.6)	39	6211	258	279	12.26	96.01	13.13	95.7	4.3
≤13	6755 (99.5)	7	6444	25	311	2.2	99.61	21.88	95.4	4.6
'Rule in pulmonary complications										
≥5	6097 (89.81)	311	685	5784	7	97.8	10.59	5.1	98.99	5.1
≥7	3970 (58.48)	267	2768	3701	51	83.96	42.79	6.73	98.19	6.73
≥9	1915 (28.21)	187	4743	1726	131	58.81	73.32	9.78	97.31	9.77
≥11	653 (9.62)	91	5909	560	227	28.62	91.34	13.98	96.3	13.94
≥13	124 (1.83)	22	6369	100	296	6.92	98.45	18.03	95.56	17.74

TP=True positive. TN=True negative. FP=False positive. FN=False negative. PPV=Positive predictive value. NPV=Negative predictive value.

Supplementary table 5. Clinical risk groups

	Derivation GlobalSurg/CovidSurg-Week N=87,806		Validation 1 CovidSurg-Cancer N=30,978		Validation 2 RECON N=6818	
Risk	Patients	PPC rate (%)	Patients	PPC rate (%)	Patients	PPC rate (%)
0-5 (Very low)	30689 (35.59)	137 (0.45)	2830 (9.28)	11 (0.39)	1825 (26.89)	27 (1.48)
6-10 (Low)	43888 (50.9)	739 (1.68)	18186 (59.64)	398 (2.19)	4311 (63.52)	200 (4.64)
11-15 (Moderate)	11027 (12.79)	813 (7.37)	9052 (29.69)	687 (7.59)	651 (9.59)	91 (13.98)
≥16 (High)	627 (0.73)	92 (14.67)	424 (1.39)	89 (20.99)	-	-

Appendix A. Full definitions of predictor variables and clinical outcomes

American Society of Anaesthesiologists physical status classification (ASA grade)

ASA grade is a validated system used to assess and communicate a patient's pre-anaesthesia medical comorbidities (1). The classification system can be used to stratify risks of postoperative complications. The following grades were defined in the study protocol:

- Grade 1: Healthy person
- Grade 2: Mild systemic disease
- Grade 3: Severe systemic disease
- Grade 4: Severe systemic disease that is a constant threat to life
- Grade 5: A moribund person who is not expected to survive without the operation.

Revised Cardiac Risk Index (RCRI)

The RCRI represents a multifactorial approach to assessing perioperative cardiac risk. It is calculated as a composite of:

- Procedural risk (intraoperative/intrathoracic versus other): in this study all patients undergoing cardiac surgery, gastrointestinal surgery, general surgery, gynaecology, hepatobiliary surgery, thoracic surgery, urology, or vascular surgery procedures scored this point.
- History of ischemic heart disease.
- History of myocardial infarction.
- History of congestive heart failure.
- History of cerebrovascular disease (stroke or transient ischaemic attack).
- History of diabetes mellitus requiring insulin use: in this study all diabetic patients scored this point.

- History of chronic kidney disease (creatinine > 176 µmol/L): in this study all patients reported to have moderate or severe chronic kidney disease scored this point.

Each item adds 1 point to the score. The total score gives an attributable risk score from 0 (lowest risk) to 6 (highest risk) (2). Patients with known Chronic Kidney Disease scored a point for this factor, even in the absence of preoperative creatinine testing in settings where this was not performed routinely.

Pre-existing respiratory disease

Pre-existing respiratory disease was defined as a formal, preoperative diagnosis of Chronic Obstructive Pulmonary Disease (COPD), asthma or interstitial lung disease.

Preoperative SARS-CoV-2 test

A preoperative SARS-CoV-2 test was defined as a reverse transcriptase polymerase-chain reaction nasopharyngeal swab test performed in the 72h before surgery. As per the inclusion criteria in this study, only patients with a negative test (or without a test nor suspicion of SARS-CoV-2 infection) were included.

Grade of surgery

Grade of surgery was categorised on the basis of the Bupa schedule of procedures as either minor (minor or intermediate according to the Bupa schedule) or major (major or complex major according to the Bupa schedule) (3).

Hospital type

The hospital type was categorised at an individual patient level at the time of surgery, according to the type of surgical pathway in which they underwent surgery (4).

- COVID-free surgical pathway if:

- the hospital admitted patients for treatment of COVID-19, but provided admission, operation and recovery areas for surgical patients that were fully segregated from COVID-19 patients, including ward, theatres and intensive care areas;
- OR if the hospital did not admit patients for treatment of COVID-19 (i.e., a dedicated 'cold'/'green'/'COVID-19 free' site for elective surgery only)
- No defined pathway if any of the areas where the patient was operated or admitted was shared with COVID-19 patients, the patients was considered to have underwent surgery in a non-segregated pathway.

Community SARS-CoV-2 risk

The community SARS-CoV-2 incidence was calculated for each participating hospital's local community. As the CovidSurg-Cancer study and the GlobalSurg-CovidSurg Week study were ran at different stages of the pandemic (January to April 2020 and October 2020, respectively), the SARS-CoV-2 risk at a global and local level was different across studies.

The community SARS-CoV-2 incidence was determined for each patient based on the 14-day case notification rate at the time of surgery in each participating country. These data were extracted from World Health Organisation (5), European Centre for Disease Prevention and Control (6), or US Centre for Disease Control and Prevention (CDC) (7) statistics using the Our World in Data portal. SARS-CoV-2 rates were calculated for two-week windows based upon the number of confirmed SARS-CoV-2 cases at the smallest available administrative level (city, region, or country) in the 14-days around the date of surgery (7-days before, 7-days after) (8).

For the patients included in the CovidSurg Cancer study, the hospitals were classified as being in communities with either low (< 25 cases per 100,000 population) or high (\geq 25 cases per

100,000 population) SARS-CoV-2 incidence. For the patients included in the GlobalSurg-CovidSurg Week study, the case cut-off per 100,000 used to define low and high-risk areas was 100 cases per 100,000 population, reflecting changes in access to testing and reporting between February and October 2020.

Country income

Country level income was defined according to the World Bank index classification (updated in 2019) based on Gross National Income per capita, which determines three income groups: high income; upper-middle income; lower middle-income (including patients from both low and lower-middle income countries).

Postoperative pulmonary complications

The primary outcome was postoperative pulmonary complications (PPCs), which was defined as a composite of postoperative pneumonia, acute respiratory distress syndrome (ARDS) and unexpected ventilation. This outcome has been used in previous CovidSurg studies, having been adapted from the PRISM randomised controlled trial (4, 9-13).

The PPC rate was the primary outcome in all three studies; however, in the RECON study, two additional complications (atelectasis and pulmonary aspiration) were included in the primary outcome definition (full StEP-COMPAC criteria (14)). Definitions were harmonised before data processing began (i.e., atelectasis or pulmonary aspiration only not classified as an event).

Unexpected postoperative ventilation was defined as any episode of non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation after initial extubation after surgery; or patient could not be extubated as planned after surgery.

Acute respiratory distress syndrome (ARDS) was defined as an acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue with hypoxemia and bilateral radiographic opacities. The Berlin consensus definition was used (15).

Postoperative pneumonia was recorded according to the US Center for Disease Control (CDC) definition of pneumonia, modified to accommodate limited availability of radiological facilities at some participating centres. Patients were required to have at least one of the following:

- Fever ($>38^{\circ}\text{C}$) with no other recognised cause;
- Leucopenia (white cell count $<4.10^9$) or leucocytosis (white cell count $>12.10^9$);
- For adults >70 years old, altered mental status with no other recognised cause;

AND at least two of the following:

- New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements;
- New onset or worsening cough, or dyspnoea, or tachypnoea;
- Rales, crackles or bronchial breath sounds;
- Worsening gas exchange (hypoxaemia, increased oxygen requirement).

The following chest radiograph findings were considered to confirm pneumonia: new or progressive and persistent infiltrates; consolidation; or cavitation.

In the event of reoperation within 30-days, the clock continued to 30-days from the index procedure i.e., the clock did not reset from the time of the reoperation. By definition any reoperation for a postoperative complication would be ineligible, so any one patient could only be included once in a study.

Training materials for primary outcome assessment were provided in the GlobalSurg-CovidSurg week study and COVIDSurg-Cancer study within the study protocol, and through site initiation webinars, that were launched live and then made available open-access on a dedicated YouTube® channel. In this study, all investigators were postgraduate clinicians regularly involved in the diagnosis and care of PPCs. In the RECON study (which also included medical student investigators), a dedicated training platform was established including five modules in study delivery and governance. A dedicated module provided training on PPC diagnosis and treatment for investigators, who had to pass a short evaluation before starting data collection.

Appendix B. Independent PROBAST assessment (16)

Version of 15/05/2019

Step 1: Specify your systematic review question

State your systematic review question to facilitate the assessment of the applicability of the evaluated models to your question. *The following table should be completed once per systematic review.*

State your systematic review question to facilitate the assessment of the applicability of the evaluated models to your question. <i>The following table should be completed once per systematic review.</i>	
Criteria	Specify your systematic review question
<i>Intended use of model:</i>	Prognosis, Risk of pulmonary complications in adults undergoing elective surgery to support safe surgery during pandemic recovery (CovidSurg-Pulmonary Score)
Participants <i>including selection criteria and setting:</i>	Adult patients (≥ 18), undergoing planned elective surgery (no restriction to operation type, approach, or indication for surgery). Patients with suspected or confirmed SARS – COV2 as well as those with local excision or endoluminal surgery were excluded.
Predictors (used in modeling) <i>including (1) types of predictors (e.g. history, clinical examination, biochemical markers, imaging tests), (2) time of measurement, (3) specific measurement issues (e.g. any requirements/ prohibitions for specialized equipment):</i>	<ul style="list-style-type: none"> • Patient demographics (Age, Sex, American Society of Anaesthesiologist grade, revised Cardiac risk index score, pre-existing respiratory disease, smoking status), • Disease factors: compartment (thoracic / abdominopelvic / head & neck / limb / other), indication (benign / cancer), preoperative SARS-CoV-2 test (not-performed / negative). • Operation factors: anaesthetic type (general / regional or local), operation grade (minor / major, defined according to the BUPA operation severity classification system (3)) • Location factors: hospital type (COVID-19 free surgical pathway / no defined pathway), community SARS-CoV-2 risk (low / high, based on the 14-day cumulative case notification rate in the area of the hospital around the date of surgery (4, 10)), country income (high / upper-middle / low-middle (including both lower-middle and low-income countries), according to the World Bank classification). Due to differences in detection of SARS-CoV-2 with the availability of facilities for testing and notification across income settings, we pre-planned to handle and interaction between these two location factors by creating a stratified factor of community SARS-CoV-2 risk by income (11, 17, 18).
Outcome <i>to be predicted:</i>	Postoperative pulmonary complications within 30-days of surgery – with day 0 as day of surgery.

Step 2: Classify the type of prediction model evaluation

Use the following table to classify the evaluation as model development, model validation or model update, or combination. Different signalling questions apply for different types of

prediction model evaluation. If the evaluation does not fit one of these classifications then PROBAST should not be used.

Classify the evaluation based on its aim			
Type of prediction study	PROBAST boxes to complete	Tick as appropriate	Definition for type of prediction model study
Development only	Development	✘	Prediction model development without external validation. These studies may include internal validation methods, such as bootstrapping and cross-validation techniques.
Development and validation	Development and validation	✓	Prediction model development combined with external validation in other participants in the same article.
Validation only	Validation	✘	External validation of existing (previously developed) model in other participants.

This table should be completed once for each publication being assessed and for each relevant outcome in your review.

Publication reference	N/A
Models of interest	GSU-Pulmonary Score
Outcome of interest	Postoperative pulmonary complications within 30-days of surgery

Step 3: Assess risk of bias and applicability

PROBAST is structured as four key domains. Each domain is judged for risk of bias (low, high or unclear) and includes signalling questions to help make judgements. Signalling questions are rated as yes (Y), probably yes (PY), probably no (PN), no (N) or no information (NI). All signalling questions are phrased so that “yes” indicates absence of bias. Any signalling question rated as “no” or “probably no” flags the potential for bias; you will need to use your judgement to determine whether the domain should be rated as “high”, “low” or “unclear” risk of bias. The guidance document contains further instructions and examples on rating signalling questions and risk of bias for each domain.

The first three domains are also rated for concerns regarding applicability (low/ high/ unclear) to your review question defined above.

Complete all domains separately for each evaluation of a distinct model. Shaded boxes indicate where signalling questions do not apply and should not be answered.

DOMAIN 1: Participants
A. Risk of Bias
DEV: This study was an international, prospective, multicentre cohort study of all consecutive patients undergoing surgery between 5 October 2020 and 1 November 2020. Any centre around the world performing inpatient surgery was eligible for inclusion. Participating centres could include patients from one or more specialty groups, so long as consecutive sampling was performed. This included both elective and emergency surgery, patients of all ages, and undergoing all operation types and for any condition.

VAL Dataset1: CovidSurg-Cancer was an international, prospective cohort study of adult patients with a diagnosis of surgically curable cancer with a decision for surgery during the SARS-CoV-2 pandemic (i.e., from the emergence of COVID-19 up to 31 August 2020). Any hospital worldwide that performed elective cancer surgery in an area affected by the COVID-19 pandemic was eligible. Data from the 15 most common operated, solid tumour types were collected with colleagues collaborating across 10 surgical oncology disciplines.

VAL Dataset2: RECON was a prospective multi-centre, international cohort study on pulmonary complications after major abdominal surgery for adults. Eligible patients were identified by local collaborators at each participating hospital during two data collection periods: 1 January to 30 April 2019 (UK and Republic of Ireland), and 1 September to 31 October 2019 (Australia). Consecutive adult patients undergoing a broad range of major abdominal surgeries were eligible across four surgical disciplines (abdominal visceral resection, reversal of stoma, open vascular surgery, anterior abdominal wall hernia repair, or transplant surgery through any operative approach). Planned day case procedures and abdominal surgeries without visceral resection were excluded.

	Dev	Val
1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Y	Y
1.2 Were all inclusions and exclusions of participants appropriate?	Y	Y
Risk of bias introduced by selection of participants	RISK: (low/ high/ unclear)	Low

Rationale of bias rating:

DEV: Cohort study for development of the model included all patients that underwent surgery, no concern of eligibility criteria, those with likely SARS-COV2 were excluded. Consecutive series of patients included.

VAL Dataset 1: Included all adult patients undergoing 15 most common (elective) cancer surgery during the pandemic. No issue with eligibility criteria.

VAL Dataset 2: Consecutive eligible adult patients were included. No issues with eligibility criteria, it seems reasonable.

B. Applicability

Describe included participants, setting and dates:

DEV: This study was an international, prospective, multicentre cohort study of all consecutive patients undergoing surgery between 5 October 2020 and 1 November 2020. Any centre around the world performing inpatient surgery was eligible for inclusion.

VAL Dataset 1: CovidSurg-Cancer was an international, prospective cohort study of adult patients with a diagnosis of surgically curable cancer with a decision for surgery during the SARS-CoV-2 pandemic (i.e., from the emergence of COVID-19 up to 31 August 2020).

VAL Dataset 2: Eligible patients were identified by local collaborators at each participating hospital during two data collection periods: 1 January to 30 April 2019 (UK and Republic of Ireland), and 1 September to 31 October 2019 (Australia). Consecutive adult patients undergoing a broad range of major abdominal surgeries were eligible across four surgical disciplines.

Concern that the included participants and setting do not match the review question	CONCERN: (low/ high/ unclear)	Low	Low
<i>Rationale of applicability rating:</i> Included patients appear to be from wide geographical, as well as different types of surgery. Included patients are representative of the population specified in the review question. Patients and setting seem to fit review question.			

DOMAIN 2: Predictors

A. Risk of Bias

List and describe predictors included in the final model, e.g. definition and timing of assessment:
Patient demographics: (Age, Sex, American Society of Anaesthesiologist grade, revised Cardiac risk index score, pre-existing respiratory disease, compartment (thoracic / abdominopelvic / head & neck / limb / other), indication (benign / cancer), anaesthetic type (general / regional or local), operation grade (minor / major, defined according to the BUPA operation severity classification system), community SARS-CoV-2 risk (low / high, based on the 14-day cumulative case notification rate in the area of the hospital around the date of surgery), country income (high / upper-middle / low-middle (including both lower-middle and low-income countries), according to the World Bank classification). Due to differences in detection of SARS-CoV-2 with the availability of facilities for testing and notification across income settings, we pre-planned to handle and interaction between these two location factors by creating a stratified factor of community SARS-CoV-2 risk by income.
 DEV: All the variables were recorded when patient were included in the cohort study.
 VAL: All variables were collected at baseline timepoint as cohort study.

	Dev	Val
2.1 Were predictors defined and assessed in a similar way for all participants?	Y	Y
2.2 Were predictor assessments made without knowledge of outcome data?	Y	Y
2.3 Are all predictors available at the time the model is intended to be used?	Y	Y

Risk of bias introduced by predictors or their assessment	RISK: (low/ high/ unclear)	Low	Low
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Rationale of bias rating:
 DEV & VAL: No major issues identified, standard definitions were used and circulated to all participating hospitals. Acceptable rationale provided to input SARS-CoV-2 risk as low (no risk) in pre-pandemic dataset.

B. Applicability

Concern that the definition, assessment, or timing of predictors in the model do not match the review question	CONCERN: (low/ high/ unclear)	Low	Low
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Rationale of applicability rating:
 All predictors were measured at baseline and defined in standard way. They appear to match the review question. One of the datasets is pre-pandemic and SARS-COV2 status is not available but assumed to be low, which is an appropriate assumption.

DOMAIN 3: Outcome

A. Risk of Bias

Describe the outcome, how it was defined and determined, and the time interval between predictor assessment and outcome determination:

DEV: The primary outcome measure was postoperative pulmonary complications (PPC) within 30-days of surgery, with day 0 as the day of surgery. This was defined as a composite of pneumonia, acute respiratory distress syndrome and unplanned use of invasive or non-invasive mechanical ventilation.

VAL: The primary outcome measure was postoperative pulmonary complications (PPC) within 30-days of surgery, with day 0 as the day of surgery. This was defined as a composite of pneumonia, acute respiratory distress syndrome and unplanned use of invasive or non-invasive mechanical ventilation.

	Dev	Val	
3.1 Was the outcome determined appropriately?	Y	Y	
3.2 Was a pre-specified or standard outcome definition used?	Y	Y	
3.3 Were predictors excluded from the outcome definition?	Y	Y	
3.4 Was the outcome defined and determined in a similar way for all participants?	Y	Y	
3.5 Was the outcome determined without knowledge of predictor information?	PN	PN	
3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Y	Y	
Risk of bias introduced by the outcome or its determination	RISK: (low/ high/ unclear)	Low	Low
<p><i>Rationale of bias rating:</i> Training of outcome assessors and detailed definitions provided in appendix. PPC primary outcome in all three studies, but subtly different outcome definition in RECON study – this was harmonised before analysis and detailed in full in appendix.</p> <p>The composite outcome is largely objective, and the prior knowledge of predictor information unlikely to cause bias in this context. Almost impossible to blind e.g., patient sex or operation grade to a clinical assessor. Assessment of radiology (required by diagnostic criteria for component outcomes would have been fully blinded ie., an independent radiologist.</p>			
B. Applicability			
<i>At what time point was the outcome determined:</i>			
Outcome was determined 30 days after surgery			
<i>If a composite outcome was used, describe the relative frequency/distribution of each contributing outcome:</i>			
Outcome is composite of			
Concern that the outcome, its definition, timing or determination do not match the review question	CONCERN: (low/ high/ unclear)	Low	Low
<i>Rationale of applicability rating:</i> This is good match to review question, timing as well as the outcome are same in all studies.			

DOMAIN 4: Analysis
Risk of Bias
<p><i>Describe numbers of participants, number of candidate predictors, outcome events and events per candidate predictor:</i></p> <p>DEV: 86231 with 1781 events and 13 predictor variables. VAL: 30488 with 1185 events in CovidSurg-Cancer and 6789 in RECON with 318 events</p>
<p><i>Describe how the model was developed (for example in regards to modelling technique (e.g. survival or logistic modelling), predictor selection, and risk group definition):</i></p> <p>Candidate predictor variables were identified in a systematic review of existing risk scores and refined with multidisciplinary clinical input from surgery, anaesthesia and critical care experts. In order to improve adoption of the risk stratification tool, we planned to only include predictor variables that are available globally without the need for additional tests, and that were relevant to resource-limited environments. All the predictor parameters were included in two models. The first model consisted of a penalised logistic regression model, the least absolute shrinkage and selection operator (LASSO) where logistic regression with an extra penalty term shrinks covariate coefficients towards zero, allowing for the generation of sparse models and concurrently performing feature selection (19). The second model applied was gradient boosting decision trees (XGBoost), which is commonly recognised as a best-in-class machine learning algorithm. XGBoost can acknowledge more complex interactions and so is hypothesized to obtain better predictive capabilities (20). However, because of its complexity, the ability to explain and understand predictive reasoning is hindered ('black box machine learning'). Hyperparameters of learning rate, maximum tree depth, loss reduction and minimum number were tuned, with trees set to 1000.</p> <p>The derivation set was split into a random 75 (training) and 25 (testing) split, and both models were fit through 10-fold cross-validation and parameter tuning using tune race analysis of variance (ANOVA) and ten random parameters in the training set. Given the class imbalance predicted <i>a priori</i> (i.e., estimated PPC rate typically between 1% and 20% depending on case-mix), for model fitting both the F statistic and AUROC were optimised.</p>
<p><i>Describe whether and how the model was validated, either internally (e.g. bootstrapping, cross validation, random split sample) or externally (e.g. temporal validation, geographical validation, different setting, different type of participants):</i></p> <p>During the model selection phase, model performance and feature importance were compared between the two model. Performance was estimated using the model discrimination, which describes models' ability to rank patients based on risk. Discrimination was evaluated using the area under the receiver operating characteristic curve (AUROC), analogous to the C-Statistic. Confidence intervals were assessed from the cross validated models. Variable importance was assessed for both modelling approaches to better understand the model's decision making (21). Final model selection was balanced between (in order of priority): (1) performance; (2) interpretation and explainability; (3) the number of predictor variables (i.e., fewer predictor variables assumed to be easier to adopt into clinical practice). If the LASSO model was selected, we planned to refit this model using resampling (2000 bootstraps) with coefficients were averaged across all resamples (22, 23)</p> <p>The performance of the final model after internal validation (named hereafter the 'CovidSurg-Pulmonary Score') was assessed using both discrimination and calibration measures. Discrimination was presented with 95% confidence intervals calculated by bootstrap</p>

<p>resampling (2000 samples). Calibration, measuring the agreement between predicted and observed risk, was examined through both the brier score, calibration in the large (slope and intercept) and visualized through reliability diagrams across deciles of risk. We assessed the CovidSurg-Pulmonary Score's performance (discrimination and calibration) in the external datasets, overall and in three pre-planned subgroups of high clinical importance: (1) major versus minor operation grade, low (ASA grade 1-2) versus high (ASA grade ≥ 3) risk, and high versus low-middle country income (including UMIC, LMIC and LIC). To aid in the interpretation of the external validation we explored whether reproducibility or transportability was being evaluated (24). In brief, this analysis has three phases. First, assessing the relatedness of datasets with the C-statistic of a 'membership model'. Second, comparing model performance in the derivation and validation sets (discrimination, calibration in the large, calibration slope). Third, interpretation of external validation results.</p>				
<p><i>Describe the performance measures of the model, e.g. (re)calibration, discrimination, (re)classification, net benefit, and whether they were adjusted for optimism: AUROC for discrimination and brier score Bootstrapping and cross validation</i></p>				
<p><i>Describe any participants who were excluded from the analysis: DEV: The overall rate of missing data was very low (<0.1% overall) VAL: The overall rate of missing data was very low (<0.1% overall)</i></p>				
<p><i>Describe missing data on predictors and outcomes as well as methods used for missing data: Complete case analysis was used as missing data was low for all candidate predictor variables. Appropriate reference provided.</i></p>				
		Dev	Val	
4.1	Were there a reasonable number of participants with the outcome?	Y	Y	
4.2	Were continuous and categorical predictors handled appropriately?	Y	Y	
4.3	Were all enrolled participants included in the analysis?	PY	PY	
4.4	Were participants with missing data handled appropriately?	Y	Y	
4.5	Was selection of predictors based on univariable analysis avoided?	Y		
4.6	Were complexities in the data (e.g., censoring, competing risks, sampling of controls) accounted for appropriately?	PY	PY	
4.7	Were relevant model performance measures evaluated appropriately?	Y	Y	
4.8	Were model overfitting and optimism in model performance accounted for?	Y		
4.9	Do predictors and their assigned weights in the final model correspond to the results from multivariable analysis?	Y		
Risk of bias introduced by the analysis		RISK: <i>(low/ high/ unclear)</i>	Low	Low
<p><i>Rationale of bias rating: EPV might be little low for machine learning approach, internal validation and restricted regression approaches used.</i></p>				

There are very few patients excluded from analysis (less than 2% MAR) with a comparison provided in supplementary table. Both bootstrapping and cross validation done with LASSO, although random split has also occurred. Appropriate statement included RE: managing death as a competing risk.

Step 4: Overall assessment

Use the following tables to reach overall judgements about risk of bias and concerns regarding applicability of the prediction model evaluation (development and/or validation) across all assessed domains.

Complete for each evaluation of a distinct model.

Reaching an overall judgement about risk of bias of the prediction model evaluation	
Low risk of bias	If all domains were rated low risk of bias. If a <u>prediction model was developed without any external validation</u> , and it was rated as low risk of bias for all domains , consider downgrading to high risk of bias . Such a model can only be considered as low risk of bias, if the development was based on a very large data set <u>and</u> included some form of internal validation.
High risk of bias	If at least one domain is judged to be at high risk of bias .
Unclear risk of bias	If an unclear risk of bias was noted in at least one domain and it was low risk for all other domains.

Reaching an overall judgement about applicability of the prediction model evaluation	
Low concerns regarding applicability	If low concerns regarding applicability for all domains, the prediction model evaluation is judged to have low concerns regarding applicability .
High concerns regarding applicability	If high concerns regarding applicability for at least one domain, the prediction model evaluation is judged to have high concerns regarding applicability .
Unclear concerns regarding applicability	If unclear concerns (but no “high concern”) regarding applicability for at least one domain, the prediction model evaluation is judged to have unclear concerns regarding applicability overall.

Overall judgement about risk of bias and applicability of the prediction model evaluation		
Overall judgement of risk of bias	RISK: (low/ high/ unclear)	Low
<p><i>Summary of sources of potential bias:</i></p> <p>DEL: Model was developed on a large prospective, cohort study. Large dataset with a sufficient number of events. Complete case analysis was performed, but the frequency of missing was low, and appears MAR. LASSO was used and optimisation was used.</p> <p>VAL: Model was validated on a two prospective cohort studies. Reasonably large number of events. Complete case analysis was performed, but the frequency of missing was low.</p>		
Overall judgement of applicability	CONCERN:	Low

	(low/ high/ unclear)	
<i>Summary of applicability concerns:</i> As all domain low concerns regarding applicability.		

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