AUTHOR ACCEPTED MANUSCRIPT

Exploratory analysis of pre and postoperative risk stratification tools to identify acute kidney and myocardial injury in patients undergoing surgery for chronic subdural haematoma

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To the Editor

Perioperative statistical risk stratification is widespread. Such tools inform intraoperative and postoperative care as part of the National Emergency Laparotomy Audit (NELA)[1].

Patients with chronic subdural haematomas (cSDH) are often elderly with significant comorbidity[2]. Despite this, there is a paucity of literature pertaining to risk stratification models in this cohort[3]. At our centre, as part of a multidisciplinary improvement initiative (the 'Improving Care in Elderly Neurosurgery Initiative' (ICENI)[4]) (Project ID:PRN7705) we demonstrated a significant association between postoperative complications and length of stay[2]. As a further analysis within this cohort of operated cSDH, we explore the potential of using retrospective electronic health record (EHR) data to generate prognostic statistical models for the identification of two end-organ complications (myocardial injury –troponin above the upper limit of normal and acute kidney injury (AKI) –a rise in serum creatinine of $\geq$ 1.5 times baseline). Outcomes were chosen based on data availability and veracity as well as clinical relevance. The integrated nature of our EHR permitted incorporation of variables reflecting intraoperative management. This enabled an exploratory analysis of models that, analogous to NELA, could be used preoperatively and updated postoperatively.

Logistic regression models were built using variables available prior to (age, American society of Anesthesiologists (ASA) score, creatinine, antithrombotic use, inter-hospital transfer, pre-operative physiological state, and comorbidities), and end of (opioid dose, length of wait, time with mean arterial pressure, (MAP) <80mmHg, time with end tidal carbon dioxide ($ETCO_2$) outside of 3-5kPa, and volatile *v* intravenous anaesthetic maintenance), surgery. Physiological state was encapsulated on each admission day using the electronic postoperative morbidity score (ePOMS)[5](details in *supplemental digital content*). Full details of variable generation are published elsewhere[2]. Missing data was handled by multiple imputation[6]. This was used in two ways. Firstly, *m=40* imputed datasets were formed to permit univariable screening (carrying forward all with p <0.2) and sequential simplification of the multivariable model using pooled likelihood ratio tests (LRT). These models were subsequently internally validated using *k*-fold (*k=10*) cross-validation using a 'fold then impute' strategy to minimise bias[7]. Model building and LRT results are in *Supplemental Digital Content.* All analysis was conducted in R v3.5.3[8].

This study utilised a previously identified, retrospective cohort of 531 consecutive cases of primary operation for cSDH between October 2014 and January 2019, with appropriate outcome data[2]. 53 individuals suffered myocardial injury, 24 AKI. 69 had at least one 'end-organ' complication. After multivariable model building (*See Supplemental Digital Content Figure S2)* an admission model containing ASA, an indicator of tertiary transfer, anti-thrombotic use, and admissions ePOMS score was formed (**Model 1** in **Table 1**). These were supplemented with significant day of surgery variables and the process repeated. The resulting model contained ASA, tertiary transfer, anti-thrombotic use, day of surgery ePOMS, intraoperative fentanyl dose, and time out of $ETCO_2$ range (**Model 2** in **Table 1).** Models yielded AUCs of 0.81(SD=0.01) and 0.85 (SD=0.01) after cross-validation (*Supplemental Digital Content Figures S3 and S4).*

Our work, despite being a single centre study and lacking external validity, demonstrates the possibility of using routinely-collected data to generate statistical models for the identification of postoperative complications after cSDH surgery. The retrospective nature of our data and the limitations of diagnostic and operative coding in cSDH[2] means we have not been able to include all potentially relevant explanatory variables (e.g. severity of cSDH). This is one of many challenges in developing prognostic models in cSDH. For instance, the apparent protective association for transferred patients reflects right censoring, due to the absence of complication data after discharge from our centre. Improved data linkage between centres is required to accurately generate models to predict complications in such patients.

Our pre-surgery model could be calculated in any centre as the increment in discriminatory performance in model 2, although statistically significant, is likely clinically unimportant. For example, the apparent protective association with fentanyl dose could be identifying a subset of patients, deemed able to tolerate higher doses by their anaesthetist. The increased odds seen with variation in $ETCO_2$ could represent patients with low cardiac output or raised intracranial pressure (requiring hyperventilation).

Further work in larger cohorts, with appropriately linked outcome data, is required to validate our approach and build on the exploratory analysis reported here to determine clinical utility.

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Supplemental Digital Content Files

File 1: Supplementary Word File (.docx)

File 2: Supplementary Figure 2 (.pdf)

File 3: Supplementary Figure 3 (.pdf)

File 4: Supplementary Figure 4 (.pdf)

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Exploratory analysis of pre and postoperative risk stratification tools to identify acute kidney and myocardial injury in patients undergoing surgery for chronic subdural haematoma.

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Contents:

1) **Cohort details and missing data**
2) **Calculation of an electronic postoperative morbidity score (ePOMS)**
3) **Approach to the handling of missing data**
4) **Univariable screening**
5) **Model building process (incl. excluded variables and *p* values)**
6) **R Code (github link)**

Section 1: Cohort details and missing data

Full details of patterns of missing data and the cohort's characteristics have been previously published and are available here and summarised briefly below.

Of note in our previously published study one patient had missing formal discharge data (and thus an inaccurate length of stay). In this study we had necessary laboratory results (and thus outcome data) to include them, giving us a total cohort of *n* = 531.

Variable	Median [IQR]
Age *years*	77 [69-84]
Creatinine $\mu mol/l$	73 [61-89]
	n (%)
Male	376 (70.8)
ASA $\geq$ 3	271 (61.0)*
Cognitively Impaired	270 (54.5)*
Admission GCS 15	342 (64.4)
Admission Motor Score 6	490 (92.3)
mRS $\geq$ 2	105 (31.0)*
Anticoagulants/Antiplatelets	233 (43.9)
CVS Disease	239 (45.0)
Heart Failure	101 (19.0)
Airways Disease	75 (14.1)

*ASA = American society of anesthesiologists score, GCS = Glasgow Coma Scale, mRS = Admission Modified Rankin Score, CVS = Cardiovascular, Motor score refers to score on the motor (movement) component of the GCS. * indicates that value is calculated only on those with recorded values (see missing data)*

Four variables had missing data;

- Baseline creatinine (*n*= 46 - 8.7%)
- Cognitive status (*n*= 36 - 6.8%),
- ASA score (*n*= 87 - 16.1%),
- mRS (*n*= 192 - 36.2%)

Patterns of missing data:

- mRS alone (*n = 133* – 25.0%)
- ASA alone (*n = 46* – 8.7%)
- Creatinine + mRS (*n = 13* – 2.4%)
- Creatinine alone (*n = 10* – 1.9%)
- Cognitive status + mRS (*n = 10* – 1.9%
- Cognitive Status alone (*n = 9* – 1.7%)
- Creatinine + ASA (*n = 6* – 1.1%)
- Cognitive status, creatinine, mRS (*n = 5* – 0.9%)
- Cognitive status + Creatinine (*n = 4* – 0.8%)
- Cognitive status + creatinine + ASA (*n = 3* – 0.6%)
- Creatinine ASA + mRS (*n = 3* – 0.6%)
- Cognitive status + ASA + mRS (*n = 3* – 0.6%)
- Cognitive status + ASA + mRS + Creatinine (*n = 2* – 0.4%)
- Cognitive status + ASA (*n = 1* – 0.2%)

Section 2: Calculation of an electronic postoperative morbidity score (ePOMS)

Domain	Diagnostic Criteria	Notes
Respiratory	Need for supplementary oxygen	
Cardiovascular	HR >100 SBP <100 Positive Troponin test	
Neurological	Need for nurse special	Nurse special used as surrogate for confusion/delirium
	Motor/Verbal Score worse than referral*	Motor/Verbal Score refers to specific domains of the GCS
	Focal neurology*	Documented mismatch between left/right sided arm/leg strength at any stage
Renal	Rise in creatinine to $\geq$ 1.5x baseline	Baseline creatinine taken as last recorded creatinine prior to surgery.
GI	Anti-emetic administered	Anti-emetic defined by following WHO ATC codes: a04**, a03fa01, r06ae03, n05ad08
Pain	Need for IV opioids or local anaesthetic infusion	Drugs identified by following WHO ATC codes: n02aa01i, n02ab03i, n01bb01
Recurrence[%]	Reoperation	EPOMS originally identifies severe wound infection by need for further surgery. In this context reoperation for the same procedure is being used to identify re-accumulation of cSDH
Infection	Temperature $\geq 38^{o}$C Receiving Antibiotics	Antibiotics defined by following WHO ATC codes: j01**
Haematological	Transfused with blood product	Including red cells, platelets, FFP, cryoprecipitate

*HR = Heart Rate, SBP = Systolic blood pressure, GCS = Glasgow Coma Scale, GI = Gastrointestinal system, WHO ATC = World Health Organisation Anatomical therapeutic chemical classification, IV = intravenous, FFP = fresh frozen plasma. If multiple potential criteria are listed then an individual scores if any of these are met % In the original EPOMS score this would correspond to the 'wound' category. * Indicates additional criterion included in this variant from previously published*[1]. *** indicates that all drugs below this level of ATC code were included*

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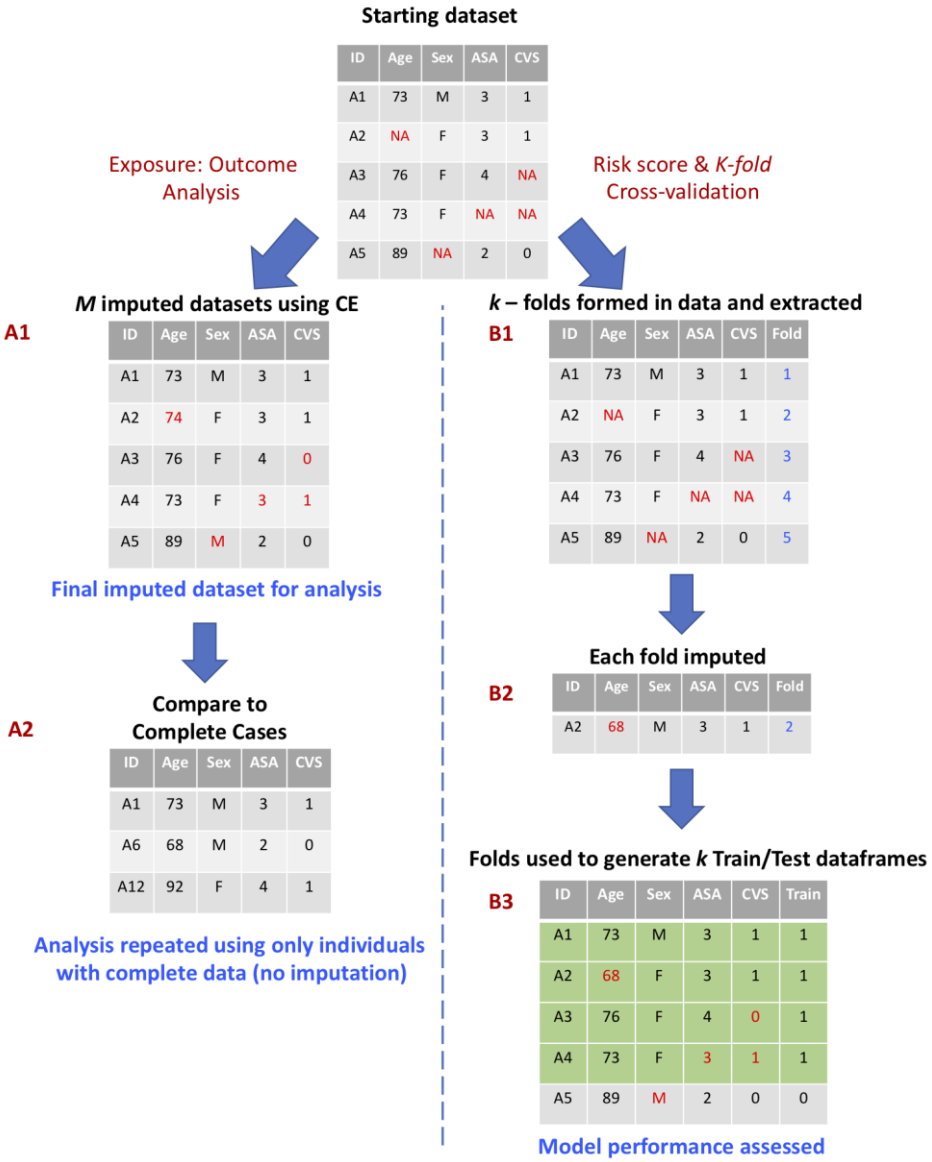
Section 3: Approach to the handling of missing data



Supplementary Figure S1: Approach to the handling of missing in data in model building (A1-A2) and in combination with *k-fold* cross validation for internal validation of generated model.

For assessment between exposures (variables) and outcome of interest, missing baseline variables were imputed using `multiple imputation using chained equations' (MI with CE) (**A1**). These results were compared to complete cases results for each analysis (**A2**). A distinct approach was used to allow internal validation of final multivariable models. This was done with *k=10* fold cross-validation. The dataset was split into test/train folds (**B1**), test folds were then individually imputed (**B2**), before being recombined (**B3**). Fold indices

created in **B1** were use d to perform cross validation forming sequential training (green rows) and test (grey row) datasets.

Section 4: Univariable screening

	OR	95% Lower	95% Upper	*p*
Age *per year*	1.002	0.982	1.024	0.819
Male *versus Female*	0.641	0.378	1.086	0.099
ASA2 *All versus ASA 1*	0.848	0.097	7.373	0.881
ASA3	3.126	0.405	24.137	0.275
ASA4	13.260	1.612	109.067	0.017
ASA5	0.832	0.000	3.000	0.999
mRS 1 *All versus mRS 0*	1.042	0.500	2.171	0.913
mRS 2	1.337	0.524	3.407	0.544
mRS 3	1.846	0.674	5.056	0.234
mRS 4	0.892	0.259	3.071	0.856
Tertiary transfer *versus direct admission*	0.340	0.161	0.720	0.005
Cognitive Impairment	3.005	1.640	5.506	<0.001
M6 on admission *versus any other motor score*	0.244	0.121	0.493	<0.001
GCS 15 on admission *versus any other GCS*	0.396	0.237	0.661	<0.001
Creatinine *per 20μmol/l*	1.127	1.020	1.269	0.031
History of CVS Disease	2.410	1.426	4.072	0.001
Anticoagulant on admission	4.359	2.468	7.699	<0.001
Airways Disease	2.755	1.516	5.008	0.001
Heart Failure	1.920	1.083	3.404	0.026
Admission EPOMS *per 1 domain increase*	1.513	1.290	1.775	<0.001
DOS EPOMS *per 1 domain increase*	1.668	1.379	2.017	<0.001
Pre-op Deterioration	0.613	0.367	1.023	0.062
Length of Wait *per hour*	1.005	1.000	1.011	0.069
Op Time *per 10 min*	1.062	1.001	1.127	0.057
Volatile anaesthetic *versus TIVA*	0.964	0.579	1.606	0.889
Fentanyl dose *per 25 mcg*	0.839	0.758	0.928	<0.001
Time MAP not 80mmHg *per 10 min*	0.961	0.886	1.041	0.346
Time CO2 not 3-5kPa *per 10 min*	1.293	1.116	1.509	0.001

Supplementary Table S1: Pooled univariable analysis for the identification of end-organ complications (myocardial infarction or acute kidney injury) in a cohort of 531 cases of operated chronic subdural haematoma. Analysis conducted across m = 40 multiply imputed datasets. *ASA = American Society of Anesthesiologists score, CO2 = End Tidal Carbon Dioxide tension, CVS = Cardiovascular System, DOS = Day of Surgery, EPOMS = Electronic postoperative morbidity score, GCS = Glasgow Coma Scale, kPa = kilopascals, MAP = mean arterial pressure, mcg = micrograms, min = minutes, M6 = Motor score of 6 on the Glasgow coma scale, mRS = Modified Rankin Scale, TIVA = Total Intravenous Anaesthesia, Length of wait = wait between admission and surgery.*

Section 5: Model building process and results for identification of end-organ complications:

After a process of univariable screening, all variables with *p<0.2* were carried forward to multivariable model building. This was performed by pooling results across 40 multiply imputed datasets and compared to complete cases.

Supplementary Figure S2 demonstrates model building process. After univariable testing a starting model formed from variables available to clinicians **prior to surgery** and the subsequent order of exclusion of variables using backwards step regression with a threshold for exclusion of *p=0.05* on the pooled likelihood ratio test.

This final `pre-op model' **(Model 1 in Table 1)** was then further refined by the addition of information available at the conclusion of surgery (DOS = Day of Surgery variables) with an equivalent process of model refinement using backwards step regression. This resulted in a final `post-op model' (**Model 2 in Table 2).**

Both models were subsequently tested using internal validation with a distinct imputation method (see **Supplementary Figure S1**) and discrimination assessed using the area under the receiver operator characteristic curve (ROC) (**Supplementary Material Figures S3 and S4)**

Section 6: R Code

Although data for this cannot be made available due to its potentially sensitive nature and origins within an approved service evaluation project we have made our analytical code available on GitHub here.

Supplementary Figure S2:
Summary of Multivariable model building

Starting model:

	OR	95% Lower	95% Upper	p
Male	0.610	0.331	1.119	0.110
ASA	1.670	0.953	2.926	0.073
M6 on Admission	0.720	0.276	1.882	0.502
GCS15 on Admission	0.747	0.388	1.439	0.383
Cognitive Impairment	1.727	0.810	3.682	0.157
CVS Disease	1.843	0.929	3.657	0.080
Creatinine	1.127	0.961	1.321	0.090
Airways Disease	1.580	0.758	3.290	0.221
Heart Failure	0.769	0.359	1.645	0.497
Anticoagulant	2.867	1.526	5.384	0.001
Tertiary Transfer	0.455	0.168	1.230	0.120
Admission ePOMS	1.256	1.048	1.506	0.014

Sequential removal of variables based on *p*

Variable removed	*P prior to removal*	*P (LRT to previous)**
M6 on admission	0.502	0.501
Heart Failure	0.519	0.519
GCS15	0.222	0.195
Airways Disease	0.196	0.206
Male	0.114	0.144
Creatinine	0.130	0.150
Cognitive Concern	0.086	0.074
CVS Disease	0.069	0.066

ASA, Tertiary Transfer, Anticoagulation, Admission ePOMS carried forward

Add in DOS variables:

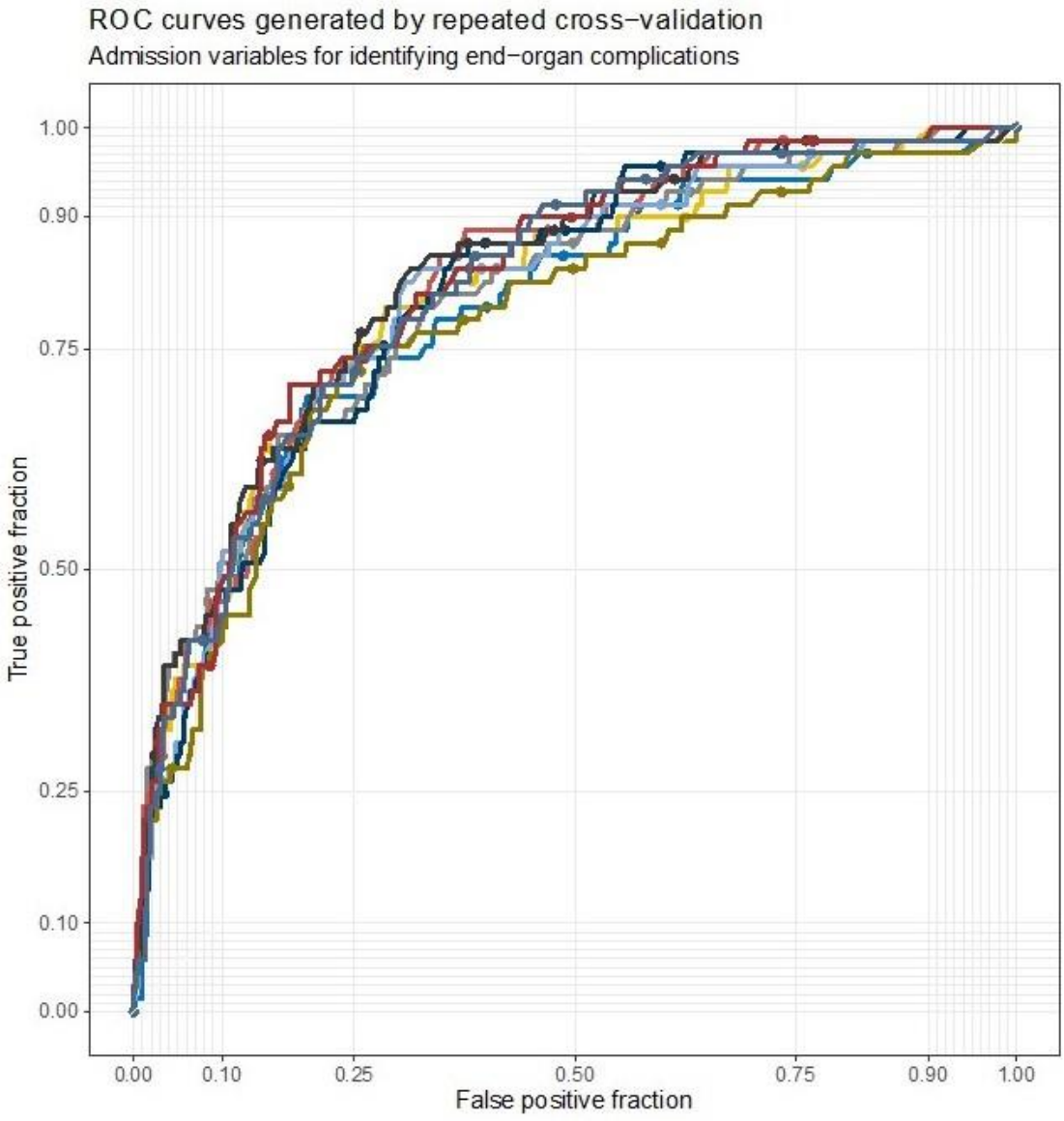
	OR	95% Lower	95% Upper	p
ASA	1.890	1.107	3.225	0.022
Tertiary Transfer	0.304	0.116	0.796	0.015
Anticoagulant Use	3.450	1.793	6.637	<0.001
Admission ePOMS	1.200	0.984	1.458	0.071
DOS ePOMS	1.300	1.035	1.630	0.024
Operation time (per 10 min)	1.020	0.944	1.104	0.603
Fentanyl dose (per 25mcg)	0.840	0.764	0.940	0.002
Time MAP <80mmHg (per 10 min)	0.949	0.856	1.053	0.325
Time outside of $ETCO_2$ 3-5kPa (per 10 min)	1.308	1.072	1.594	0.008
Length of Wait (per hr)	1.005	0.999	1.011	0.120

Sequential removal of variables based on *p*

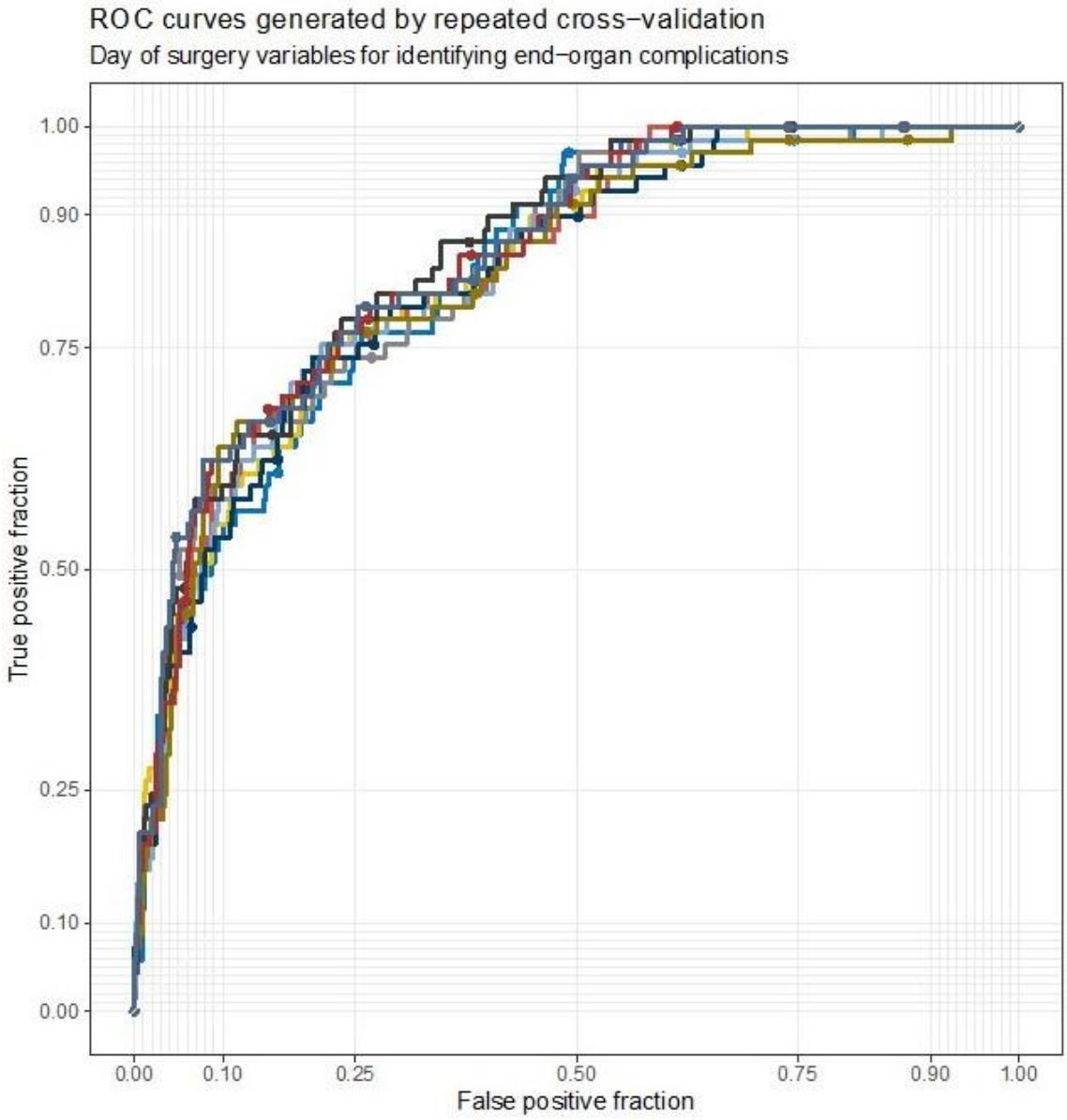
Variable removed	*P prior to removal*	*P (LRT to previous)**
Operation time	0.603	0.599
Time MAP <80mmHg	0.399	0.388
Length of Wait	0.126	0.129
Admission ePOMS	0.120	0.116

Final model: ASA, Anticoagulant use, DOS ePOMS, Fentanyl dose, Time out of CO2 range, Tertiary Transfer.

Supplementary Figure S3: Receiver Operator Characteristic (ROC) curve for model using admission variables



Supplementary Figure S4: Receiver Operator Characteristic (ROC) curve for model using day-of-surgery variables



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