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Routinely measured hematological markers can help to predict AIS scores following spinal cord injury

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Abstract

Neurological outcomes following spinal cord injury (SCI) are currently difficult to predict. Whilst the initial American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade can give an estimate of outcome, the high remaining degree of uncertainty has stoked recent interest in biomarkers for SCI. This study aimed to assess the prognostic value of routinely measured blood biomarkers by developing prognostic models of AIS scores at discharge and 12-months post-injury. Routine blood and clinical data were collected from SCI patients (*n*=417) and blood measures that had been assessed in less than 50% of patients were excluded. Outcome neurology was obtained from AIS and Spinal cord independence measure III (SCIM-III) scores at discharge and 12-months post-injury, with motor (AIS) and sensory (AIS, touch and prick) abilities being assessed individually. Linear regression models with and without elastic net penalization were created for all outcome measures. Blood measures associated with liver function such as alanine transaminase were found to add value to predictions of SCIM-III at discharge and 12-months post-injury. Furthermore, components of a total blood count including hemoglobin were found to add value to predictions of AIS motor and sensory scores at discharge and 12-month post-injury. These findings corroborate the results of our previous preliminary study and thus provide further evidence that routine blood measures can add prognostic value in SCI, and that markers of liver function are of particular interest.

Keywords: Spinal cord injury; blood; biomarker; neurology; modelling

Introduction

Spinal cord injury (SCI) is damage to the spinal cord due to trauma, degeneration or disease that results in a temporary or permanent change to its neurological function. The global age-standardized incidence of SCI has been estimated to be 13 per 100,000, whereas the age-standardized prevalence was estimated to be 368 per 100,000.[1] With respect to the United Kingdom, it has been estimated that over 1000 new SCIs occur each year, and that 40,000 people are living with SCI.[2] The majority of SCIs have historically been traumatic in nature, most commonly as a result of vehicular accidents, falls, violence and sports, but more recently non-traumatic SCI, usually as a result of infection or cancer, has been increasing in prevalence.[3,4]

The lifetime cost of SCI in the UK is estimated to be £1.12 million (mean value) per case, with the total cost of SCI in 2016 in the UK being £1.43 billion.[5] SCI can lead to secondary conditions that increase morbidity and mortality, including respiratory complications, deep vein thrombosis, muscle spasms, urinary tract infections, osteoporosis, pressure ulcers, risk of fracture, and chronic pain. Furthermore, patients with SCI are often rendered dependent on caregivers and show markedly higher rates of mental illness relative to the general population.[6]

There is a challenge in the development of novel therapeutic interventions for SCI, with only four large-scale clinical trials having been tested in acute SCI, three of which evaluated methylprednisolone and one evaluated GM-1 ganglioside.[7–10] This is due to the SCI population being inherently heterogeneous and experiencing a highly variable degree of "natural" recovery.[11] Currently, the best predictor of neurological outcome is the initial measure of neurologic impairment, as assessed with the International Standards for Neurological Classification of SCI (ISNCSCI) examination.[12] However, the ISNCSCI exam was not intended to be predictive of functional recovery, and it has been found that changes in American Spinal Injury Association Impairment scale (AIS) grade do not necessarily indicate meaningful changes to daily living for patients.[13] Robust SCI biomarkers could help stratify patients such that their baseline functional recovery could be predicted, allowing any potential novel therapies to be properly assessed, thus accelerating research and clinical trials in particular via covariate adjustment.[14] A reliable prognostic model of SCI would also

allow healthcare providers to better plan patient care, relieve patients of potentially damaging psychological uncertainty, and could highlight new avenues of research.[15] Whilst relatively few studies have sought to identify prognostic biomarkers for SCI, recent years have seen some early/discovery phase publications.[16–19] These preliminary studies have largely focused on biomarkers in cerebral spinal fluid during the acute phase of injury, with little information regarding the chronic or recovery phase. Even among these studies however, there has been little investigation as to the value of blood biomarkers in SCI at any injury phase, despite success in other fields, including cancer, traumatic brain injury, and Alzheimer's disease.[20–22]

We previously published a preliminary study that highlighted the value of routinely measured blood analytes in prognostic models of SCI, and demonstrated that some blood measures, particularly markers of liver function, added modest, but statistically significant, value to predictions of 3- and 12-month ISNSCI AIS motor and sensory scores.[23] In this study, we have validated our findings in another, independent and larger SCI cohort. We have further developed alternative more robust methods of modelling and have demonstrated that similar markers, including alanine transaminase (ALT) and gamma-glutamyl transferase (GGT) add value not only when predicting AIS scores at discharge and 12-months, but also with regards to SCIM outcomes.

Method

Patient and model feature summary

We retrospectively studied the electronic health records of 500 patients who had been admitted to the Midlands Centre for Spinal Injuries (MCSI) in the last 10 years (Table 1). Access to these records was ethically approved by the National Research Ethics Service [NRES] Committee North West Liverpool East [11/NW/0876] and NRES Committee West Midlands, Staffordshire [13/WM/0158]. Following the exclusion of patients that had been admitted over 6 months post-injury, 73 individuals were removed from further analysis.

The remaining 417 patients had their initial blood sample taken at a mean of 31 ± 30 (standard deviation) days post-injury. Blood measures that had been assessed in less than

50% of the patient cohort were excluded. The remaining blood measures included adjusted calcium estimate, alkaline phosphatase, C-reactive protein (CRP), hematocrit, hemoglobin, mean cell hemoglobin, mean cell volume, mononucleocytes, platelets, potassium, red blood count, red blood distance width and white blood count (WBC). Routine blood analyses were conducted in the Hematology and Biochemistry department located at the Robert Jones and Agnes Hunt Orthopedic Hospital. Hematology analyses were performed on either a Beckman Coulter LH-500 (Beckman Coulter, High Wycombe) or a Sysmex XN-1000 (Sysmex America, IL). Biochemical analyses used VITROS slides (dry multi-layered chemistry slides) in conjunction with the VITROS 5,1 FS Chemistry System (Ortho Clinical Diagnostics, New Jersey, USA) to measure albumin, ALT, calcium, creatinine, GGT, potassium, magnesium, sodium, total bilirubin, total protein, and urea.

In addition to AIS overall grade, AIS motor, sensory touch and sensory pin prick scores were recorded at admission, discharge (mean 136 days post-injury ± 72) and approximately 12 months post-injury (mean 424 days post-injury ± 147). Spinal cord independence measure III (SCIM-III) assessments were also recorded at these same time points.[24] The SCIM assessment is a disability scale developed to quantify the ability of SCI patients to perform basic activities of independent daily living, including self-care (feeding, bathing and dressing), respiration and sphincter management, and mobility (Figure 1).[25,26]

Additional information that may impact neurological recovery and/or the assessed blood measures were included. The incidence of diabetes (types I and II), smoker and alcohol drinking status were recorded as binary. The neurological level of the injury was recorded as being cervical, thoracic, lumbar or sacral. Details were recorded as to whether the injury was traumatic, and whether there were any fractures at the injury site. Age at injury in years, gender and the time between injury and the first blood tests in days were also included. Medications that patients were prescribed were also collected, however after filtering to drugs at least 50% of patients were given, the remaining drugs were either painkillers or anti-spasm medication. As the inclusion of this drug data would have added a large number of variables to the model, and they correlated strongly with initial injury severity, this data was not included in the modelling process.

Model building

Data analyses were performed with the statistical programming language R version 3.6.3 (2020-02-29).[27–40] Missing blood measures were median imputed, then scaled and centered. Less than 21% of the initial and discharge AIS/SCIM scores were missing, whereas 50-60% of the 12-month scores were missing (Table S1). These missing AIS grades or scores were imputed with either last observation carried forwards (LOCF) or next observation carried backwards (NOCB) where relevant. LOCF and NOCB were used as it is unusual for AIS or SCIM scores to have decreased over time in SCI patients. These scores typically only either remain largely unchanged, or improve with time.[41] Therefore, the use of this imputation effectively assumes that in cases of missing score data, the patients' score did not change. This assumption can only worsen model performance, as opposed to giving rise to the overly optimistic models that could be generated by more complex multiple imputation techniques. Additionally, we have been advised that most cases where neurological assessment was missing at admission or discharge is due to a transition from Frankel scoring to AIS. In the case of missing 12-month assessments, this is most commonly due to a given patient not attending their appointment or having received follow up from a different hospital (Table S1).

As the number of model features was relatively high compared to the number of observations (45 features and 417 observations), linear regression with elastic net penalization was performed in addition to linear regression without any penalization. Elastic net penalization is a hybrid of ridge regression, whereby the penalty term shrinks predictor effect equally and never to 0, and least absolute shrinkage & selection operator (LASSO), whereby the penalty term shrinks each predictor differently and allows variables to be removed entirely by shrinking coefficients to 0.[42,43] Put simply, elastic net reduces the impact of less important model features and can effectively eliminate features entirely, thus performing variable selection during the model building process, as opposed to other methods such as backward variable selection, which are conducted before model building and eliminate features based on co-linearity. Elastic net penalization has been previously found to perform well in models with numerous predictors and in the presence of correlated predictors.[44]

Eight independent models were generated, with and without elastic net penalization, to determine if the features could predict four outcome measures: AIS motor, AIS sensor touch, AIS sensor prick and SCIM, at two time points: discharge and 12-months post-injury. The data was randomly split 80-20%, whereupon 80% was used for training the model and the remaining 20% was used to test the models performance. To reduce model optimism, internal validation was performed by 10-fold cross validation.[45]

Results

Multiple regression models of the AIS motor and sensory scores, and of SCIM, at discharge (mean 136 ± 72 days post-injury) and approximately 12 months post injury (mean 424 ± 147 days post-injury) were built (Tables S2, S3 & S4). In addition to standard linear regression models (LRM), generalized linear models (GLM) with elastic net penalization were also performed. The modelling techniques performed similarly (GLM R^2 range $0.56 - 0.79$ and RMSE range $11 - 18$, LRM R^2 range 0.53-0.76 and RMSE range 12-19) (Figures 1 & 2)

Model features

With respect to model features, AIS measures of initial neurological function were the most consistently conserved features and the most powerful predictors of outcome measures for the generalized models. Initial SCIM was also included for all the models of outcome, except those relating to discharge sensory prick, touch and 12-month sensory touch. The blood markers, ALT, albumin, alkaline phosphatase, CRP, creatinine, GGT, hematocrit, hemoglobin, mean cell hemoglobin, mean cell volume, monocytes, platelets, potassium, total bilirubin, total protein, urea and WBCwere significant (P-Value < 0.05)/included in one or more models (Table 2).

For the linear regression models, the AIS grade on admission was the only feature that was statistically significant (P-Value < 0.05) in all models except 12-month SCIM. The initial measure of the model target, so the initial AIS motor score for the models of discharge and 12 month AIS motor for example, was also significant in all models. Other significant features that were not blood measures included diabetes and smoker status, age at injury,

time until first blood test from injury, the neurological level of injury, gender, and the presence of fracture at the injury site. Regarding blood measures, urea, monocytes, mean cell hemoglobin, mean cell volume, hematocrit and hemoglobin were all significant in one or more of the models (Table 2).

Model performance

With respect to model predictions, both modelling techniques performed similarly when predicting against the test data (Figures 3 & S1-8).

Discussion

Penalized GLM was compared to linear regression in the study due to the sample size. Whilst there has long been a dogma that 10 events per variable (EPV) is sufficient, more recent studies have argued that there is no rational for this.[46,47] As there were 417 patients and 45 variables, we also investigated the impact of modelling with and without variable selection in the form of elastic net penalization.

In this study, a standard linear regression model with no variable selection performed very similarly to GLM with elastic net penalization with respect to R^2 and RMSE, though the R^2 of GLM was slightly higher and RMSE slightly lower for all model targets (Figures 1 & 2). This suggests that elastic net penalization does not provide a substantial boost to overall model performance at this sample size relative to linear regression. However, there was a difference in the variables each model utilized.

Regarding blood measures in the linear regression models, urea, total bilirubin and creatinine were significant predictors for one or more outcomes. Creatinine was predictive of discharge SCIM and sensor touch. Total bilirubin was predictive motor, sensor prick and sensor touch at month-12, suggesting it is predictive of longer term outcomes. Urea, which is typically used as an indicator of kidney function, but may also be altered due to hydration status, was predictive of discharge SCIM in the standard linear regression model, but was predictive of month-12 sensor touch in the penalized models.

With the exception of time to first blood test from injury, all of the same features were included in the penalized models and the linear regression models, but other related bloods were also included, such as mean cell hemoglobin, mean cell volume, hematocrit, hemoglobin, platelets and WBC, which are the components of a complete blood count. The complete blood count is likely related to the initial injury severity via blood loss due to bony soft tissue or visceral injury, gastrointestinal bleeding, and/or surgery.[48] Monocytes were included in all GLM models at both time points except month-12 SCIM. Similar to the components of the complete blood count, monocytes levels may be indicative of anemia (if low), but have also been associated with hepatitis and inflammatory diseases (if high).[49,50] Estimated serum creatinine, based on glomerular filtration rates, are typically used in the evaluation of renal function.[51,52] SCI patients have also been found to have an increased risk of renal deterioration and are recommended to receive lifelong, regular renal and upper urinary tract examinations after injury.[53,54] SCI has been found to lead to systemic inflammation which can in turn cause secondary organ complications, including in the liver, kidneys and lungs, which may explain why these blood measures are useful in predicting outcome.[55-58]

Some studies have found SCI to induce hepatic lipid deposition and inflammation, within 3 months of injury in rats, which is symptomatic of non-alcoholic steatohepatitis (NASH), the hepatic presentation of metabolic syndrome.[59,60] Importantly, the blood measures associated with liver function (alanine transaminase, alkaline phosphatase, CRP, GGT and total bilirubin) highlighted in this study were also found to be significantly predictive of AIS scores in our preliminary study. Two factors “liver function”, consisting of alanine transaminase, alkaline phosphatase and GGT and “liver function and inflammation” consisting of CRP and total bilirubin added statistically significant value to models of AIS touch and pain scores at 3-months post injury, and AIS motor and pain scores at 12-months.[23,61,62] Total bilirubin in particular was included in 5 out of 8 penalized models and was significant in 3 of the non-penalized models. This provides further evidence that liver function is relevant to neurological recovery in SCI.

Interestingly, alanine transaminase, alkaline phosphatase, GGT and albumin were only retained in the models of SCIM. This could be because these markers indicate liver status,

which in turn typically reflects general metabolic health. Therefore, aberrant ALT and GGT values may be a proxy measure of poor metabolic health or systemic inflammation. Diabetes status was also significant in 6 of the 16 models built in this study, which may also reflect the relevance of general metabolic health in recovery. Metabolic syndrome is also more common in SCI patients than the general population and, SCI patients consequently have an increased risk of diabetes, stroke and heart disease.[60,63–65]

Serum albumin has also been previously found to be significantly predictive of AIS grade improvement up to 52 weeks.[66] Platelets and gender were also only retained in models of SCIM. Previous studies contradict this result and have suggested that gender does not significantly correlate with functional neurology or independence.[67,68] However, it may be that some elements of the SCIM questionnaire are easier for males, such as self-catheterization, and so they are able to obtain slightly higher scores than females, even at a similar level of neurological function (as determined by AIS scores). Interestingly, surgery was only found to be a significant predictor of SCIM at both time points in the GLM models. This suggests surgery does not have a substantial influence on AIS outcomes. It should be stressed that this hospital favors a conservative approach to care of SCI patients, only choosing to operate in the most extreme cases and so both the rate and type of surgery given to this cohort likely differ from other spinal centers.[69] Therefore, external validation with data from centers with the more common surgical approach to SCI care is needed to more fully establish the role of surgery in predicting outcomes.[70, 71]

Whether the injury was traumatic or not was not retained in any model. Despite the very distinct pathophysiology of non-traumatic injuries, this data suggests trauma status is not a strong predictor of AIS motor or sensor score outcomes.[72] Prior studies have also observed similar functional outcomes between traumatic and non-traumatic injuries.[73] Further research is needed to establish the role of the liver in SCI, particularly whether the liver is causally implicated in functional recovery, or if it is merely a proxy indicator of systemic inflammation inhibiting healing. Once this association is established, clinicians could consider monitoring the liver function of SCI patients more closely, perhaps attempting to restore/maintain healthy parameters in the interim by minimizing the use of hepatotoxic drugs where possible.

An important limitation of this study is the volume and completeness of the data used in model building. A larger sample size will always lead to a more robust and widely applicable model, and whilst there was enough to build linear regression models, a larger dataset (>5000) could allow for robust logistic regression models to predict a change in AIS grade. Furthermore, the data used here contained missing values, and whilst these were imputed to have minimal effect on model performance, it is still preferable to have a complete dataset. Models of 12-month outcomes were built using discharge and admission scores with the same methodology, and whilst these models performed better overall, the proportion of missing values at the 12-month time point, sample size and more modest difference in average AIS score between discharge and 12-months may cause overfitting, therefore this data was not included. Finally, an independent external validation of these models on separate data, potentially with a cohort with more typical surgical based care, would be desirable, particularly for the GLMs as it is difficult to obtain robust estimates of bias in penalized regression, making standard errors and confidence intervals inappropriate.[74]

Conclusion

The results from this study suggest that routinely measured blood analytes can provide useful prognostic information for AIS scores and SCIM assessments up to 12-months post-injury, reinforcing the findings of our preliminary study.[23] Markers of liver function are of particular interest, and rehabilitation clinicians should consider the maintenance of liver health as a priority as it may be relevant to neurologic functional recovery. More research is needed to establish whether or not the relationship between SCI recovery and liver function is causal. Ultimately these finding need to be validated on a larger independent cohort before any firm clinical recommendations can be made.

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Author Disclosure Statement

No competing financial interests exist

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Table 1. Patient demographics

		Number of SCI patients (n out of 417)	**Percent**
	Age at injury (Median years)	56±28	
	Length of stay (Median days)	100±66	
	Fracture	225	53
	Surgery	217	51
	Traumatic injury	319	75
	Type 1 diabetes	5	1
Smoker	Type 2 diabetes	44	10
	No	281	66
	Yes	52	12
Alcohol consumption	Unknown	84	20
	No	181	42
	Yes	152	36
Gender	Unknown	84	20
	Male	283	66
Time from injury (Median	Female	134	31

days)	First blood test	22±35	
	Admission	20±34	
	Discharge	128±82	
Neurological level of injury	Month-12 assessment	390±103	
	Cervical	244	57
	Lumbar	30	7
	Sacral	1	0
Admission AIS grade	Thoracic	142	33
	A	108	25
	B	48	11
	C	151	35
	D	110	26
AIS conversion	A-B	4	0.9
from admission to 12-Months	A-C	4	0.9
	A-D	1	0.2
	B-C	11	2.6
	B-D	4	0.9
	C-D	47	11

	C-E	1	0.2
	D-E	1	0.2
AIS conversion from admission to discharge	A-B	4	0.9
	A-C	4	0.9
	B-C	13	3
	B-D	4	0.9
	C-D	47	11
	D-E	3	0.7

Table 2. Counts of model feature occurrence. For unpenalised linear regression (LRM) statistically significant (P-value < 0.05) features are included. For penalised models (GLM) features that were not penalised to 0 are induced

Model feature	**GLM**	**LRM**
(Intercept)	8	8
Admission AIS gradeB	2	2
Admission AIS gradeC	6	6
Admission AIS gradeD	6	6
Age at injury	2	2
Alanine Transaminase (u/L)	2	0
Albumin (g/L)	1	0
Alkaline Phosphatase (u/L)	1	0
C-Reactive Protein (mg/L)	1	0
Creatinine (umol/L)	4	2
Drinking yes	5	1
Fracture	1	1
Gamma GT (u/L)	1	0
Haematocrit (L/L)	4	0
Haemoglobin (g/L)	5	0
Initial motor	8	6
Initial scim	4	2

Initial sensor prick	8	2
Initial sensor touch	5	3
Lumbar injury	2	0
Mean Cell Hb (pg)	4	0
Mean Cell Volume (fL)	6	0
Monocytes (10*9/L)	7	0
Neuro level T	1	0
Platelets (10*9/L)	1	0
Potassium (mmol/L)	1	0
Sex	2	1
Smoker status known	1	0
Smoker status unknown	0	1
Surgery	1	0
Time to first blood test (Days)	0	2
Total Bilirubin (umol/L)	5	3
Total Protein (g/L)	1	0
Type 1 diabetes	2	0
Type 2 diabetes	3	1
Urea (mmol/L)	1	1
White blood count (10*9/L)	1	0

Figure 1. Boxplots of AIS score change from admission

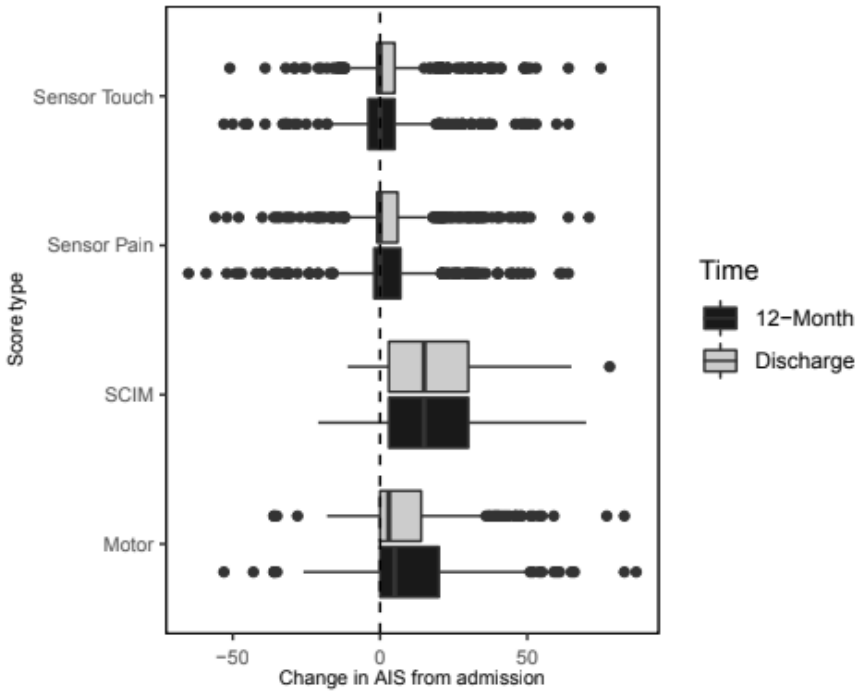


Figure 2. R^2 for models of neurological outcome at discharge and 12 months post-injury.

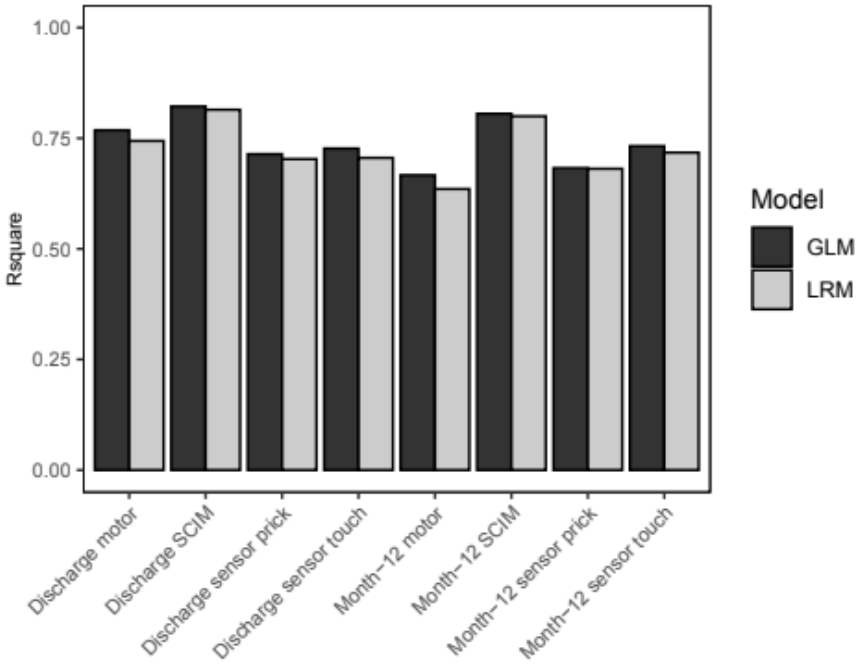


Figure 3. Root mean square error (RMSE) for linear regression models with and without elastic net penalisation (GLM and LRM respectively) of neurological outcome at discharge and 12 months post-injury.

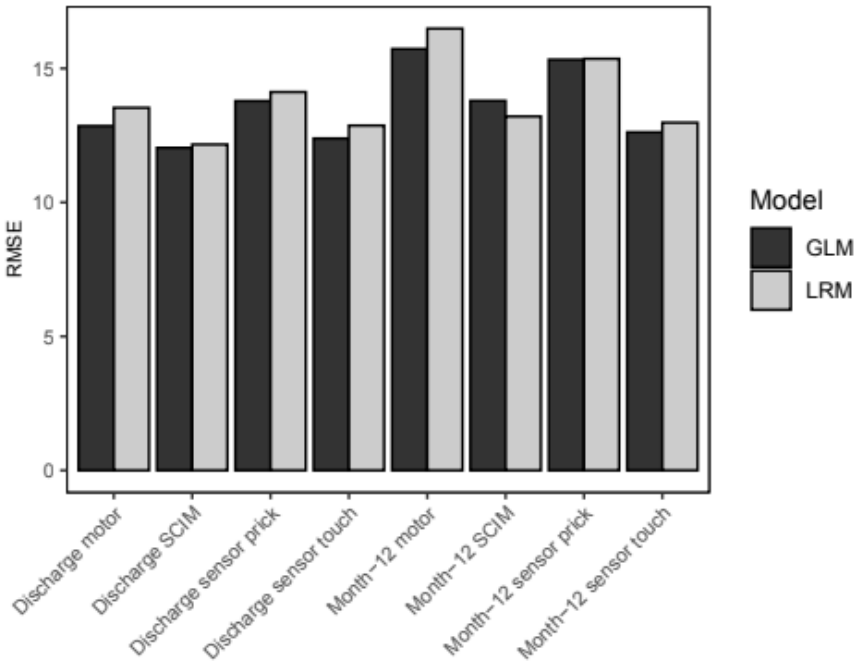
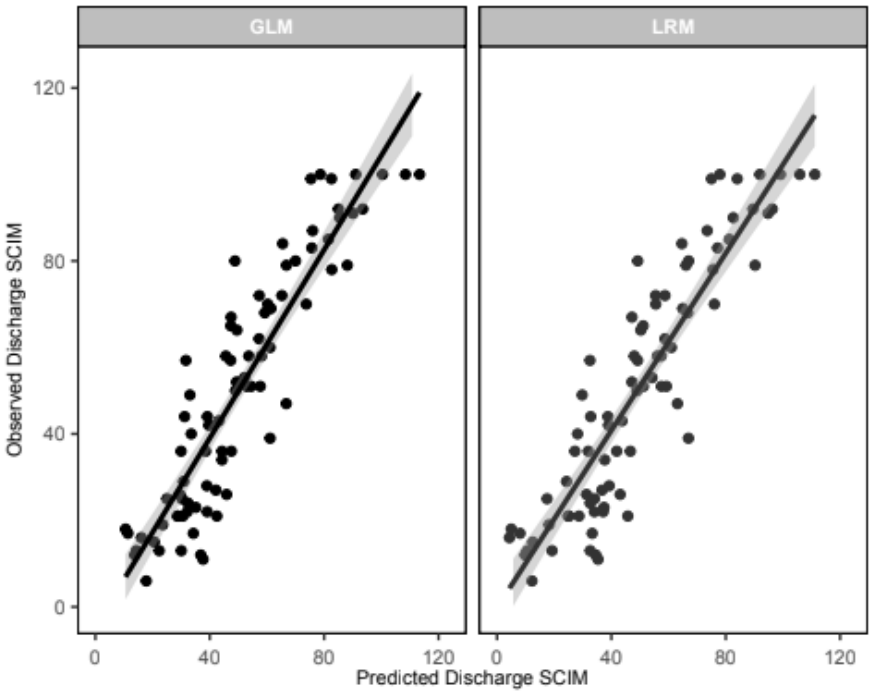


Figure 4. Predicted SCIM score at discharge compared to the observed SCIM scores in the test data.



Supplementary Table 1. Missing AIS and SCIM scores (out of 431 total patients).

	Total number of missing values	Percent missing
Initial sensor prick	3	1
Initial sensor touch	3	1
Initial motor	4	1
Discharge scim	37	9
Initial scim	44	11
Discharge motor	73	18
Discharge sensor prick	87	21
Discharge sensor touch	87	21
Month-12 scim	231	55
Month-12 motor	252	60
Month-12 sensor touch	255	61
Month-12 sensor prick	256	61

Supplementary Table 2. Linear regression model coefficients with elastic net penalisation

Model	Variable	Coefficients
Discharge motor	(Intercept)	14.4
	Haemoglobin (g/L)	0.56
	Mean Cell Hb (pg)	0.343
	Mean Cell Volume (fL)	0.297
	Monocytes (10*9/L)	0.714
	Admission ASIAC	8.12
	Admission ASIAD	7.27
	Alcohol Drinking status	0.665
Discharge sensor prick	Initial motor	0.681
	Initial sensor prick	0.0847
	Initial sensor touch	0.00759
	Initial scim	0.0483
	(Intercept)	16.7
	Creatinine (umol/L)	0.215
	Haemoglobin (g/L)	0.98
	Monocytes (10*9/L)	0.936
	Total Bilirubin (umol/L)	0.961
	Type 2 diabetes	0.13

Discharge sensor touch	Admission ASIAC	5.97
	Admission ASIAD	1.51
	Initial motor	0.165
	Initial sensor prick	0.564
	Initial sensor touch	0.13
	(Intercept)	21.3
	Creatinine (umol/L)	1.05
	Haematocrit (L/L)	1.55
	Mean Cell Volume (fL)	0.225
	Monocytes (10*9/L)	1.11
	Total Bilirubin (umol/L)	0.758
Discharge SCIM	Type 2 diabetes	1.96
	Admission ASIAB	2.85
	Admission ASIAC	10.3
	Admission ASIAD	5.24
	Lumbar injury	0.489
	Alcohol Drinking status	0.046
	Initial motor	0.064
	Initial sensor prick	0.0308
	Initial sensor touch	0.654

	(Intercept)	24.1
	Alanine Transaminase (u/L)	0.743
	Albumin (g/L)	0.000168
	Alkaline Phosphatase (u/L)	0.732
	Creatinine (umol/L)	1.48
	Gamma GT (u/L)	0.189
	Mean Cell Volume (fL)	0.899
	Monocytes (10*9/L)	0.0577
	Platelets (10*9/L)	0.249
	Total Protein (g/L)	0.775
	White blood count (10*9/L)	0.697
	Type 1 diabetes	4.86
Month-12 motor	Neuro level T	0.984
	Sex	1.97
	Alcohol Drinking status	1.88
	Fracture	0.697
	Surgery	1.27
	Initial motor	0.263
	Initial sensor prick	0.0828
Month-12 sensor prick	Initial scim	0.577

	(Intercept)	20.5
	Creatinine (umol/L)	0.016
	C-Reactive Protein (mg/L)	0.868
	Haematocrit (L/L)	0.00315
	Haemoglobin (g/L)	1.64
	Mean Cell Hb (pg)	0.0101
	Mean Cell Volume (fL)	0.442
	Monocytes (10*9/L)	0.852
	Potassium (mmol/L)	0.404
Month-12 sensor touch	Total Bilirubin (umol/L)	0.386
	Type 1 diabetes	3.37
	Admission ASIAB	0.277
	Admission ASIAC	9.01
	Admission ASIAD	9.39
	Smoking yes	0.699
	Alcohol Drinking status	1.75
	Initial motor	0.576
	Initial sensor prick	0.126
	Initial scim	0.027
	(Intercept)	14.3

	Haematocrit (L/L)	0.425
Month-12 SCIM	Haemoglobin (g/L)	0.74
	Mean Cell Hb (pg)	0.209
	Monocytes (10*9/L)	0.986
	Total Bilirubin (umol/L)	1.12
	Admission ASIAC	6.03
	Admission ASIAD	1.44
	Lumbar injury	1.45
	Age at injury (Median years)	0.0507
	Initial motor	0.193
	Initial sensor prick	0.423
	Initial sensor touch	0.229
	(Intercept)	15.5
	Haematocrit (L/L)	0.779
	Haemoglobin (g/L)	0.777
	Mean Cell Hb (pg)	0.00573
	Mean Cell Volume (fL)	0.07
	Monocytes (10*9/L)	1.17
	Total Bilirubin (umol/L)	0.672
	Urea (mmol/L)	0.162

Type 2 diabetes	1.87
Admission ASIAC	8.83
Admission ASIAD	2.44
Age at injury (Median years)	0.0249
Alcohol Drinking status	0.65
Initial motor	0.0837
Initial sensor prick	0.0852
Initial sensor touch	0.632
(Intercept)	23.9
Alanine Transaminase (u/L)	0.168
Mean Cell Volume (fL)	0.136
Sex	1.47
Initial motor	0.221
Initial sensor prick	0.0909
Initial scim	0.591

Supplementary Table 3. Final elastic net model parameters. Alpha is a value between 0 and 1, where 0 is pure ridge regression, 1 is pure LASSO and values between are a mixture of both. Lambda is the shrinkage factor applied to model coefficients

Model target	alpha	lambda
Discharge motor	1	0.679
Discharge sensor prick	1	0.738
Discharge sensor touch	0.6	0.718
Discharge SCIM	0.6	0.632
Month-12 motor	1	0.636
Month-12 sensor prick	0.4	1.67
Month-12 sensor touch	1	0.722
Month-12 SCIM	1	1.47

Supplementary Table 4. Linear regression model coefficients without elastic net penalisation

Model	Variable	Estimate	Std. Error	t value	Pr(>|t|)
Discharge motor	(Intercept)	19.6	5.02	3.91	0.000117
	Admission ASIAC	12.4	2.54	4.89	1.64e-06
	Admission ASIAD	11.2	3.41	3.3	0.0011
Discharge sensor prick	Initial motor	0.705	0.0635	11.1	4.15e-24
	(Intercept)	14.8	5.21	2.85	0.00472
	Total Bilirubin (umol/L)	1.4	0.596	2.36	0.0192
	Admission ASIAC	9.91	2.64	3.76	0.000209
	Initial motor	0.21	0.0659	3.19	0.00158
Discharge sensor touch	Initial sensor prick	0.555	0.0611	9.09	1.59e-17
	(Intercept)	22.4	4.54	4.94	1.32e-06
	Creatinine (umol/L)	1.84	0.935	1.97	0.0496
	Admission ASIAB	6.96	2.46	2.83	0.00492
	Admission ASIAC	14.5	2.3	6.29	1.17e-09
	Admission ASIAD	9.96	3.09	3.23	0.00139
	Initial sensor touch	0.664	0.0537	12.4	1.67e-28
	(Intercept)	24.1	5.79	4.17	4.06e-05

	Creatinine (umol/L)	2.96	1.19	2.48	0.0138
Discharge SCIM	Urea (mmol/L)	-2.72	1.25	-2.18	0.03
	Type 2 diabetes	-6.68	2.85	-2.34	0.0198
	Admission ASIAB	-7.26	3.14	-2.32	0.0213
	Admission ASIAD	-10.6	3.94	-2.68	0.0078
	Age at injury (Median years)	-0.208	0.0616	-3.38	0.000827
	Time to first blood test (Days)	-0.109	0.0393	-2.78	0.00586
	Smoking unknown	-5.18	2.36	-2.2	0.0289
	Initial motor	0.301	0.0733	4.11	5.19e-05
	Initial scim	0.591	0.0605	9.78	1.02e-19
	(Intercept)	25.7	6.1	4.2	3.51e-05
Month-12 motor	Admission ASIAC	14.6	3.09	4.72	3.67e-06
	Admission ASIAD	15.6	4.15	3.76	0.000206
	Initial motor	0.571	0.0772	7.39	1.52e-12
	(Intercept)	13.1	5.59	2.35	0.0194
	Total Bilirubin (umol/L)	1.57	0.64	2.45	0.0149
	Admission ASIAC	11.3	2.83	3.99	8.25e-05
Month-12 sensor	Admission ASIAD	7.75	3.8	2.04	0.0422

prick	Fracture	-4.39	2.19	-2	0.0461
	Initial motor	0.209	0.0708	2.95	0.00344
	Initial sensor prick	0.434	0.0656	6.62	1.75e-10
	Initial sensor touch	0.173	0.0661	2.62	0.00922
	(Intercept)	17.6	5.33	3.3	0.00111
	Total Bilirubin (umol/L)	1.37	0.611	2.25	0.0255
	Admission ASIAC	13.8	2.7	5.1	6.06e-07
Month-12 sensor touch	Admission ASIAD	8.18	3.62	2.26	0.0248
	Drinker status	3.57	1.66	2.15	0.0321
	Initial sensor touch	0.618	0.0631	9.79	9.19e-20
	(Intercept)	20.9	6.47	3.23	0.00139
	Sex	4.73	2.2	2.15	0.032
	Age at injury (Median years)	-0.226	0.0687	-3.29	0.00111
	Time to first blood test (Days)	-0.103	0.0439	-2.36	0.0191
	Initial motor	0.275	0.0819	3.36	0.000896
Month-12 SCIM	Initial scim	0.595	0.0675	8.81	1.17e-16