Methods/Results

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Contents

1 Multiple logistic regression of GOS

In this part, the outcome variable is Glasgow outcome scale (GOS). GOS is an ordinal variable that ranges from 1 to 5 and we used three different schemes to re-categorize the original GOS scale into a new dichotomous variable. Moreover, since the GOS was measured at month 1, 3 and 6 (after discharge ?), we conducted multiple logistical regression analyses on each of the newly created GOS variables for each of these three time points. (Thus, there are total $3 \times 3 = 9$ models)

In each of the multiple logistical regression models, we included demographic and injury severity characteristics such as Age, Gender, AIS, Eye-reactivity, CT score as well as the average of those physiological information during the hospital stay such as ICP, MAP, GCS, etc. as the independent variables. Due to missing values in observations, there are total 206, 200 and 190 effective number of patients for each of the three time points respectively. The exponential value of the resulting regression coefficient is interpreted as the odds ratio of the two outcomes, e.g. death vs others, when the predictor increases one unit (if it is continuous variable) or when it is compared to the reference group (if categorical).

For coding scheme one, we can see that at all three time points, Age, average of ICP, MAP and GCS sum are all significantly related with the outcome at 0.05 significance level. While Age and average ICP are positively correlated with the outcome, the relationship between average of MAP and GCS sum and the outcome are negative. In terms of interpretation, under our first coding scheme, i.e. death coded as 1 and others coded as 0, taking Age in the first model as an example, for a patient at the first month of discharge from the hospital the odds for him/her to be dead is 1.07 (i.e. exp(0.0701)) times of the odds for another who is one year younger. Similar interpretation applies to other predictors if they are continuous; if the predictor is categorical, the comparison is between the specific category of interest and the reference level. Note that one additional significant variable in Month 3 is AIS ($p\text{-}value = 0.0453$).

Compared to coding scheme one, in scheme two both eyes active category in eye reactivity variable becomes significantly related with outcome. The sign of the coefficient for "bothactvie" is negative means that patients with both eyes reactive are more likely to stay alive, i.e. less likely to be dead, compared to those whose eyes are bot not reactive, which is the reference group.

In coding scheme three, there is only one covariate, average GCS sum, that is significantly related with the outcome at month 1; while in month 3 and 6, Age, bothactivce and average GCS sum are significantly related with the outcome.

1.1 Scheme One: death (1) vs others (2–5)

- Month 1

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	0.5897	4.2682	0.14	0.8901
Age	0.0701	0.0161	4.35	**0.0000**
Gendermale	0.3185	0.7043	0.45	0.6511
AIS	0.0462	0.0362	1.28	0.2013
oneactive	0.1550	0.9569	0.16	0.8713
bothactive	-0.6683	0.4619	-1.45	0.1480
CTD34	0.9806	0.9855	1.00	0.3197
CTM12	0.9984	0.9093	1.10	0.2722
mean_ICP	0.1131	0.0396	2.86	**0.0042**
mean_MAP	-0.0705	0.0250	-2.82	**0.0048**
mean_GCS.sum	-0.6174	0.1956	-3.16	**0.0016**
mean_SjvO2	0.0067	0.0441	0.15	0.8800
mean_CBF	0.0033	0.0209	0.16	0.8761
mean_CMRO2	0.1700	0.4642	0.37	0.7142

Table 1: Multiple logistical regression output for death vs others at Month 1 (206 observations after removing missing)

- Month 3

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-1.4268	4.4129	-0.32	0.7464
Age	0.0784	0.0170	4.63	**0.0000**
Gendermale	0.2789	0.7036	0.40	0.6918
AIS	0.0807	0.0403	2.00	**0.0453**
oneactive	0.6333	0.9977	0.63	0.5256
bothactive	-0.5409	0.4743	-1.14	0.2541
CTD34	0.7809	0.9767	0.80	0.4240
CTM12	0.8386	0.8869	0.95	0.3444
mean_ICP	0.1318	0.0437	3.02	**0.0025**
mean_MAP	-0.0780	0.0259	-3.01	**0.0026**
mean_GCS.sum	-0.6276	0.2022	-3.10	**0.0019**
mean_SjvO2	0.0294	0.0454	0.65	0.5162
mean_CBF	-0.0009	0.0204	-0.04	0.9665
mean_CMRO2	0.1520	0.4656	0.33	0.7440

Table 2: Multiple logistical regression output for death vs others at Month 1 (200 observations after removing missing)

- Month 6

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-1.1902	4.6210	-0.26	0.7967
Age	0.0807	0.0176	4.58	**0.0000**
Gendermale	0.3301	0.7073	0.47	0.6408
AIS	0.0779	0.0436	1.78	0.0743
oneactive	0.1926	1.0083	0.19	0.8485
bothactive	-0.8033	0.4901	-1.64	0.1012
CTD34	0.4829	0.9949	0.49	0.6274
CTM12	1.1309	0.9055	1.25	0.2117
mean_ICP	0.1013	0.0430	2.36	**0.0185**
mean_MAP	-0.0928	0.0279	-3.32	**0.0009**
mean_GCS.sum	-0.8080	0.2127	-3.80	**0.0001**
mean_SjvO2	0.0708	0.0473	1.50	0.1344
mean_CBF	-0.0103	0.0211	-0.49	0.6233
mean_CMRO2	0.3396	0.4749	0.71	0.4746

Table 3: Multiple logistical regression output for death vs others at Month 1 (190 observations after removing missing)

1.2 Scheme Two: bad (1, 2) vs good (3, 4, 5)

- MONTH 1

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-0.1172	3.8370	-0.03	0.9756
Age	0.0533	0.0141	3.78	**0.0002**
Gendermale	0.2514	0.6196	0.41	0.6849
AIS	0.0487	0.0385	1.27	0.2058
oneactive	0.4157	1.0378	0.40	0.6888
bothactive	-1.0725	0.4037	-2.66	**0.0079**
CTD34	0.2872	0.6701	0.43	0.6682
CTM12	0.2603	0.5533	0.47	0.6381
mean_ICP	0.0226	0.0318	0.71	0.4765
mean_MAP	-0.0301	0.0222	-1.35	0.1755
mean_GCS.sum	-0.8119	0.1736	-4.68	**0.0000**
mean_SjvO2	0.0471	0.0380	1.24	0.2155
mean_CBF	-0.0031	0.0158	-0.20	0.8435
mean_CMRO2	0.1407	0.3577	0.39	0.6940

Table 4: Multiple logistical regression output for bad vs good at Month 1 (206 observations after removing missing)

- MONTH 3

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	0.9893	4.1193	0.24	0.8102
Age	0.0557	0.0149	3.73	**0.0002**
Gendermale	0.3626	0.6529	0.56	0.5787
AIS	0.0671	0.0399	1.68	0.0922
oneactive	-0.2126	0.9409	-0.23	0.8213
bothactive	-1.0801	0.4321	-2.50	**0.0124**
CTD34	0.9005	0.8087	1.11	0.2655
CTM12	1.1277	0.7197	1.57	0.1172
mean_ICP	0.0572	0.0350	1.64	0.1018
mean_MAP	-0.0660	0.0244	-2.71	**0.0068**
mean_GCS.sum	-0.7006	0.1802	-3.89	**0.0001**
mean_SjvO2	0.0414	0.0416	1.00	0.3195
mean_CBF	-0.0131	0.0186	-0.71	0.4795
mean_CMRO2	0.1751	0.4120	0.42	0.6709

Table 5: Multiple logistical regression output for bad vs good at Month 3 (200 observations after removing missing)

- MONTH 6

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	1.3544	4.1292	0.33	0.7429
Age	0.0557	0.0151	3.69	**0.0002**
Gendermale	0.3185	0.6531	0.49	0.6258
AIS	0.0595	0.0396	1.50	0.1327
oneactive	-0.1911	0.9242	-0.21	0.8362
bothactive	-1.0087	0.4427	-2.28	**0.0227**
CTD34	0.6205	0.8089	0.77	0.4430
CTM12	0.9891	0.7166	1.38	0.1675
mean_ICP	0.0460	0.0339	1.36	0.1746
mean_MAP	-0.0648	0.0246	-2.64	**0.0084**
mean_GCS.sum	-0.7435	0.1851	-4.02	**0.0001**
mean_SjvO2	0.0437	0.0419	1.04	0.2964
mean_CBF	-0.0087	0.0185	-0.47	0.6369
mean_CMRO2	0.1160	0.4168	0.28	0.7808

Table 6: Multiple logistical regression output for bad vs good at Month 6 (190 observations after removing missing)

1.3 Scheme Three: (1, 2, 3) vs (4, 5)

- Month 1

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-3.3226	3.8661	-0.86	0.3901
Age	0.0284	0.0158	1.80	0.0718
Gendermale	0.8935	0.6260	1.43	0.1535
AIS	0.0929	0.0516	1.80	0.0720
oneactive	14.4828	1214.0781	0.01	0.9905
bothactive	-0.4344	0.4716	-0.92	0.3569
CTD34	-0.9217	0.6915	-1.33	0.1826
CTM12	0.1459	0.5246	0.28	0.7810
mean_ICP	0.0055	0.0352	0.16	0.8763
mean_MAP	0.0192	0.0260	0.74	0.4607
mean_GCS.sum	-0.4921	0.1497	-3.29	**0.0010**
mean_SjvO2	0.0251	0.0400	0.63	0.5300
mean_CBF	0.0210	0.0206	1.02	0.3094
mean_CMRO2	-0.4431	0.3945	-1.12	0.2614

Table 7: Multiple logistical regression output for (1,2,3) vs (4,5) at Month 1 (206 observations after removing missing)

- Month 3

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-5.3350	3.6813	-1.45	0.1473
Age	0.0630	0.0158	3.98	**0.0001**
Gendermale	0.6805	0.6292	1.08	0.2794
AIS	0.0320	0.0395	0.81	0.4169
oneactive	0.3247	1.3271	0.24	0.8067
bothactive	-1.1163	0.4222	-2.64	**0.0082**
CTD34	-0.0855	0.6273	-0.14	0.8915
CTM12	0.7150	0.4809	1.49	0.1371
mean_ICP	0.0433	0.0337	1.28	0.1990
mean_MAP	0.0186	0.0231	0.80	0.4211
mean_GCS.sum	-0.5554	0.1458	-3.81	**0.0001**
mean_SjvO2	0.0522	0.0369	1.42	0.1567
mean_CBF	-0.0000	0.0156	-0.00	0.9980
mean_CMRO2	-0.2186	0.3412	-0.64	0.5217

Table 8: Multiple logistical regression output for (1,2,3) vs (4,5) at Month 3 (200 observations after removing missing)

- Month 6

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-3.2957	3.7984	-0.87	0.3856
Age	0.0704	0.0167	4.21	**0.0000**
Gendermale	1.0002	0.6567	1.52	0.1277
AIS	0.0393	0.0419	0.94	0.3481
oneactive	0.8078	1.3653	0.59	0.5541
bothactive	-0.9163	0.4415	-2.08	**0.0380**
CTD34	-0.5512	0.6740	-0.82	0.4134
CTM12	0.4083	0.5150	0.79	0.4278
mean_ICP	0.0500	0.0359	1.39	0.1639
mean_MAP	-0.0075	0.0235	-0.32	0.7493
mean_GCS.sum	-0.6598	0.1594	-4.14	**0.0000**
mean_SjvO2	0.0510	0.0379	1.35	0.1784
mean_CBF	0.0013	0.0160	0.08	0.9336
mean_CMRO2	-0.2691	0.3568	-0.75	0.4508

Table 9: Multiple logistical regression output for (1,2,3) vs (4,5) at Month 6 (190 observations after removing missing)

2 LMM for ICP

In this part the outcome of interest is intracranial pressure (ICP), which is an important physiological indicator that we closely monitor to keep an eye on patients' brain health condition. ICP is monitored over time for each patient and repeated measurements were recorded. The ICP measurements within one patient are supposed to be more similar than those from different patients. To account for the correlation of the ICP measurements with the same patient, we use linear mixed model (LMM) in modeling ICP with regard to other covariates. In LMM we introduce a hypothetic unobserved hidden variable, i.e. random effect, observations from the same patient share the same random effect while observations for different patients have different values for random effect. We fit the LMMs using `R` [3] function `lmer{lme4}`[1].

In the first model, results shown in Table 10, Age, CT code, GCS.sum and MAP are significantly related with ICP value. Take MAP as an example, the coefficient of MAP means ICP value will increase by 0.06 unit corresponding to one unit increase in MAP. In the second model we add an additional variable PbtO2 into the first model, due to the missing values the effective number of observations decreases dramatically and there is only one variable, SjvO2, that is significantly related with ICP. Results can be found in Table 11. Similarly, we investigated other potential covariates to ICP, i.e. CBF and CMRO2 in model 3 and ratio of Lactate and Pyruvate respectively and the results are listed in Table 13 and Table 14.

	Estimate	Std. Error	df	t value	Pr(>|t|)
(Intercept)	8.51	2.74	946.47	3.10	**0.00**
HAI	0.01	0.00	2026.66	1.68	0.09
Age	-0.14	0.03	222.91	-4.45	**0.00**
Gendermale	1.53	1.43	222.38	1.08	0.28
onereactive	0.64	2.13	214.17	0.30	0.76
bothreactive	-1.06	0.99	212.80	-1.08	0.28
CTD34	3.22	1.45	215.46	2.22	**0.03**
CTM12	4.28	1.14	226.80	3.76	**0.00**
GCS.sum	-0.44	0.10	2037.69	-4.51	**0.00**
MAP	0.06	0.02	2032.60	4.05	**0.00**
SjvO2	0.02	0.02	1982.45	1.26	0.21
PCO2	0.04	0.04	2037.43	0.99	0.32

Table 10: Number of obs: 2050, groups: IDNo, 258

	Estimate	Std. Error	df	t value	Pr(>|t|)
(Intercept)	6.93	15.34	12.52	0.45	0.66
HAI	0.00	0.02	88.68	0.15	0.88
Age	0.27	0.38	9.11	0.71	0.50
Gendermale	7.87	11.52	9.24	0.68	0.51
bothreactives	-6.86	7.83	9.58	-0.88	0.40
CTD34	0.52	11.98	9.24	0.04	0.97
CTM12	2.17	10.78	9.08	0.20	0.84
GCS.sum	-0.15	0.31	87.60	-0.50	0.62
MAP	-0.02	0.06	87.10	-0.30	0.76
SjvO2	0.14	0.07	88.90	2.05	**0.04**
PCO2	0.08	0.12	90.28	0.69	0.49
PbtO2	0.01	0.04	89.98	0.18	0.86

Table 11: With PbtO2 added into Model one; Number of obs: 109, groups: IDNo, 16

Table 12: Number of obs: 79, groups: IDNo, 58

	Estimate	Std. Error	df	t value	Pr(>|t|)
(Intercept)	24.18	12.85	69.00	1.88	0.06
HAI	0.02	0.03	68.84	0.76	0.45
Age	-0.16	0.07	54.42	-2.23	**0.03**
Gendermale	4.62	3.94	53.41	1.17	0.25
GCS.sum	-1.35	0.58	61.83	-2.31	**0.02**
MAP	0.02	0.08	69.00	0.26	0.79
SjvO2	-0.08	0.14	66.97	-0.61	0.54
PCO2	0.15	0.15	68.33	1.04	0.30
CBF	0.02	0.08	66.61	0.31	0.76
CMRO2	-3.41	1.69	69.00	-2.02	**0.05**

Table 13: Number of obs: 79, groups: IDNo, 58

	Estimate	Std. Error	df	t value	Pr(>|t|)
(Intercept)	-8.01	19.96	13.60	-0.40	0.69
HAI	-0.06	0.03	14.74	-2.09	**0.05**
Age	-0.16	0.16	4.77	-0.98	0.37
Gendermale	6.82	9.33	6.31	0.73	0.49
bothreactive	4.04	5.59	5.64	0.72	0.50
CTD34	8.07	7.29	5.54	1.11	0.31
CTM12	1.49	6.59	6.95	0.23	0.83
GCS.sum	1.63	0.84	13.70	1.95	**0.07**
MAP	0.10	0.09	10.21	1.08	0.31
SjvO2	0.30	0.14	11.37	2.14	**0.05**
PCO2	-0.55	0.44	14.98	-1.24	0.23
L.P.Ratio	0.01	0.05	10.99	0.17	0.87

Table 14: Number of obs: 27, groups: IDNo, 14

3 Joint modelling: ICP and ICULOS

Here we are interested in the relationship between ICULOS (outcome, ICU length of stay) and ICP values (adjusted by other factors). Taking ICULOS as the outcome, we're really interested in the relationship between time to ICU discharge and other factors, including ICP. Meanwhile, since ICP measurements are repeatedly measured overtime, i.e. time dependent, we can not simply take the mean of ICP and use it as the covariate because during the ICU stay patients with higher ICP may die earlier than others that results in a short ICULOS. So we can consider those patients as censored cases to adjust the effect of higher ICP on ICULOS. Thus, we prefer to use joint modeling method [2] in which we model ICULOS as a time to event process (ICU discharge is the event) and model ICP using longitudinal modeling method simultaneously. Specifically,

$$\begin{cases} h_i(t|\mathbf{w}_i, m_i(t)) = h_0(t)\exp[\boldsymbol{\gamma}^\top \mathbf{w}_i + \alpha m_i(t)] \\ y_i(t) = m_i(t) + \varepsilon_i(t) = \mathbf{x}_i^\top(t)\boldsymbol{\beta} + \mathbf{z}_i^\top(t)\mathbf{b} + \varepsilon_i(t), \quad \varepsilon_i(t) \sim N(0, \sigma^2) \end{cases} \tag{1}$$

where t is the time to event (ICU discharge), i.e. ICULOS; $m_i(t)$ is ICP measurements for subject i at time t; $\mathbf{w}_i$ are time independent variables for subject i; $\mathbf{x}_i$ are fixed effect covariates and $\mathbf{z}_i$ are random effects covariates, they can be either time dependent or independent.

Results are shown in Table 15. In *Event Process* (left part of the table), the value corresponds to "Assoct" is the estimate for parameter α in Equation (1). Negative value means that increased ICP values leads to longer time to event (smaller hazard rate), i.e. larger value of ICU discharge. However, the association is not statistically significant when we jointly model with the *Longitudinal Process*, where the ICP is the outcome variable as shown at the right side of the tables.

	Event Process				Longitudinal Process		
	Value	Std.Err	p-value		Value	Std.Err	p-value
Age	-0.01	0.01	0.2155	(Intercept)	19.46	2.52	< **0.0001**
Gendermale	-0.03	0.31	0.9176	Age	-0.16	0.03	< **0.0001**
onereactive	-0.53	0.45	0.2478	Gendermale	3.40	1.52	**0.0251**
both reactive	0.01	0.23	0.9742	onereactive	2.74	1.44	0.0563
CTD34	-0.63	0.33	0.0565	bothreactivce	-0.81	0.86	0.3429
CTM12	-0.88	0.26	**0.0006**	CTD34	4.48	1.24	**0.0003**
Assoct	-0.02	0.02	0.3854	CTM12	4.11	1.06	**0.0001**
$\log(\xi_1)$	-7.37	0.73		HAI	0.00	0.00	0.2137
$\log(\xi_2)$	-5.61	0.63		GCS.sum	-0.33	0.12	**0.0047**
$\log(\xi_3)$	-5.46	0.64		PCO2	0.03	0.05	0.4988
$\log(\xi_4)$	-4.80	0.65		$\log(\sigma)$	2.05	0.02	
$\log(\xi_5)$	-5.02	0.67					
$\log(\xi_6)$	-4.71	0.68		D_{11}	38.11	11.29	
$\log(\xi_7)$	-4.13	0.72					

Table 15: Parameter estimates, standard errors and p-values under the joint modeling analysis. D_{ij} denote the ij-element of the covariance matrix for the random effects.

References

[1] Douglas Bates, Martin Maechler, and Ben Bolker. lme4: Linear mixed-effects models using s4 classes. 2012.

	Event Process				Longitudinal Process		
	Value	Std.Err	p-value		Value	Std.Err	p-value
Age	-0.01	0.01	0.2639	(Intercept)	20.38	2.09	< 0.0001
Gendermale	-0.04	0.31	0.9053	Age	-0.16	0.03	< 0.0001
eyereactivity1	-0.50	0.45	0.2736	Gendermale	3.45	1.51	0.0224
eyereactivity2	-0.00	0.24	0.9858	eyereactivity1	2.82	1.43	0.0485
newCTD2	-0.64	0.33	0.0534	eyereactivity2	-0.78	0.84	0.3545
newCTM	-0.91	0.27	0.0007	newCTD2	4.42	1.23	0.0003
AIS	-0.01	0.02	0.7341	newCTM	4.03	1.03	0.0001
Assoct	-0.02	0.02	0.4681	HAI	0.00	0.00	0.1592
$\log(\xi_1)$	-7.25	1.00		GCS.sum	-0.32	0.11	0.0052
$\log(\xi_2)$	-5.49	0.93		$\log(\sigma)$	2.05	0.02	
$\log(\xi_3)$	-5.34	0.93					
$\log(\xi_4)$	-4.67	0.95		D_{11}	37.80	11.19	
$\log(\xi_5)$	-4.90	0.97					
$\log(\xi_6)$	-4.60	0.96					
$\log(\xi_7)$	-4.04	0.99					

Table 16: Parameter estimates, standard errors and p-values under the joint modeling analysis. D_{ij} denote the ij-element of the covariance matrix for the random effects.

[2] Robin Henderson, Peter Diggle, and Angela Dobson. Joint modelling of longitudinal measurements and event time data. *Biostatistics*, 1(4):465–480, 2000.

[3] R Core Team et al. R: A language and environment for statistical computing. 2012.