Outcome prediction in disorders of consciousness: the role of coma recovery scale revised

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Research article

Keywords: N/A

Posted Date: March 13th, 2019

DOI: https://doi.org/10.21203/rs.2.96/v2

Version of Record: A version of this preprint was published on April 19th, 2019. See the published version at https://doi.org/10.1186/s12883-019-1293-7.

Abstract

Background: To evaluate the utility of the revised coma remission scale (CRS-r), together with other clinical variables, in predicting emergence from disorders of consciousness (DoC) during intensive rehabilitation care. Method: This is a prospective observational cohort study of consecutive 180 brain-injured patients with prolonged DoC upon admission to neurorehabilitation unit. 123 patients in a vegetative state (VS) and 57 in a minimally conscious state (MCS) were included and followed for a period of 8 weeks in the intensive care rehabilitation unit. Demographical and clinical factors were used as outcome measures. Univariate and multivariate Cox regression models were employed for examining potential predictors for clinical outcome along the time. Results: VS and MCS groups were matched for demographical and clinical variables (i.e., age, aetiology, tracheostomy and route of feeding). Within 2 months after admission in intensive neurorehabilitation unit, 3.9% were dead, 35.5% had a full recovery of consciousness and 66.7% remained in VS or MCS. Multivariate analysis demonstrated that the best predictor of functional improvement was the CRS-r scores. In particular, patients with values greater than 12 at admission were those with a favorable likelihood of emergence from DoC. Conclusions: Our study highlights the role of the CRS-r scores for predicting a short-term favorable outcome.

Background

Goal-directed fluid therapy has proven benefits for the hemodynamic stability of perioperative and shock patients. Some recent studies have reported that moderate intraoperative volume expansion, and adequate maintenance of cardiac output (CO) can reduce the complications after surgery and the time spent in the intensive care unit (ICU)[1-3]. Inappropriate fluid administration is often harmful to patients; thus, accurate detection of the patient's hemodynamics can effectively improve the patient's prognosis (such as decrease in serum lactate, the length of stay in hospital and incidence of postoperative organ complications) [4-6].

During the perioperative period, a noninvasive continuous automatic monitoring instrument is more comfortable to the patient than invasive monitoring. A pulse oximeter is a noninvasive routine intraoperative monitor in most hospitals, and it is one of the preferred instruments for bedside monitoring [7]. The Massimo pulse oximeter (Massimo Corp., Irvine, CA, USA) adds an module for monitoring of respiratory changes in the pulse oximetry plethysmographic waveform, derived from the perfusion index (PI) [8]. Pulse perfusion index (PI) is defined as pulsatile and non-pulsatile tissues ratio of absorbed light. Pleth variability index (PVI) reflects the variation of PI in the respiratory cycle.

PVI can be continuously monitored on the display screen by connecting the probe of pulse oximeter with the measuring part and avoiding light. Its basic principle is also based on the absorption of red and infrared light emitted by the pulse oxygen probe by the tissue at the measuring site.

Several trials have contributed to investigating the reliability of the PVI in predicting preload responsiveness [9-33]. On this basis, three system reviews evaluate the high accuracy of PVI[34-36]. A series of studies have shown that the PVI can reliably predict preload responsiveness during mechanical ventilation; however, some of these studies are not convincing because the sample size was less than 30 [11, 12, 17, 19, 29, 33]. Broch O et al. reported that the PVI reliably predicted preload responsiveness only in patients with high perfusion level (PI>4%) [9]. Le Guen et al supported that the accuracy of PVI is limited during kidney transplantation [22]. Moreover, Maughan BC et al. indicated that PVI also cannot reliably predict preload responsiveness during cardiac surgery [26]. The purpose of this review is to assess the reliability of the PVI to predict preload responsiveness in different mechanically ventilated patients (patients in different locations, with different types of surgery, different ages, and different methods of expansion).

Methods

Search strategy

PUBMED, EMBASE, Cochrane Library, and Web of Science databases (last updated to November 7, 2018) were searched by two reviewers independently , using the keywords as follow : (plethysmography OR pleth OR plethysmographic) AND (variability OR variation) AND (index OR indices OR indexes). The references of all reviewed articles were viewed to look for valuable studies.

Eligibility criteria

We included diagnostic trials that evaluated the reliability of the PVI to predict fluid responsiveness in patients with mechanical ventilation. If the full text of the article is not published in English, it will be excluded. We also excluded review, case report, comment, experiments on animals, or in vitro studies.

Quality assessment

Two reviewers independently assessed the quality of reviewed studies using the QUADAS-2 scale by Review Manager 5.3(Cochrane Library, Oxford, UK) [37]. Disagreement was resolved by discussion with third reviewer.

Data extraction

The study characteristics and outcomes were examined and extracted by two reviewers independently . The following data were recorded using Microsoft Excel 2016 (Microsoft Corp, Redmond, WA): first author, year of publication, characteristics of patient, place of study, number of patients studied, tidal volume, amount of fluid infusion, the f value for defining responders to preload responsiveness, true positive rate , false positive rate , false negative rate , true negative rate , best cut-off value, sensitivity, specificity, the pooled area under the curve (AUC) of receiver operating characteristics (ROC) and r value.

For further data analysis, we also assessed the pooled sensitivity, pooled specificity, receiver operating characteristics (ROC), area under curve (AUC), Youden index (sensitivity plus specificity minus one) and 95% credibility interval (CI) of them.

Statistical treatment

Data calculation and graphics synthesis is done by Stata (version 14.0). Threshold effect and nonthreshold effect both will lead to heterogeneity. We used Spearman correlation coefficient (Mixed Model) to evaluate the threshold effect and used Cochrane-Q value of the AUC to evaluate nonthreshold effect. The heterogeneity was represented by the I2 statistic: when I2□25% , it means low heterogeneity exists, when 25%□I2□50% ,it means moderate heterogeneity exists, and when I2≥50%, it means significant heterogeneity exists. Sensitivity analyses (test each article individually whether it is a source of heterogeneity) and meta-regression (patient's surgeries; patient's age; choice of patients volume expansion methods) were used to find the source of heterogeneity. We used Deeks' Funnel Plot Asymmetry Test For Diagnostic Odds Ratio to determine whether significant publication bias exists in the articles included in the analysis [38].

Results

Literature search and study characteristics

The original literature search included 1,068 articles, of which 1007 articles were excluded by reviewing title and abstracts because they were duplicates, irrelevant studies, animal experiments, conference summaries, case reports or review articles. After careful browsing of the remaining 61 studies, 31 studies were excluded because they lacked the full-text article. Four studies were excluded because the lack of relevant data on outcomes. One study was excluded because the abstract was published in English, while the full-text was published in Chinese. The retrieved ,included and excluded articles for meta-analysis are summarized in Fig. 1. Characteristics of the 25 retrieved studies are summarized in Additional file 1.

Quality assessment and Publication bias

Quality assessment of 25 retrieved studies is shown in Fig. 2 and Fig.3.

The result of Deeks' Funnel Plot Asymmetry Test for Diagnostic Odds Ratio is that the P value=0.76, indicates that there is no significant publication bias in the included literature.

Results of retrieved studies

The results of each retrieved studies are shown in Additional file 2. Twenty-five studies that included 1035 patients. The best cut-off value for PVI varied between 7% and 20%, while 1 study [18] did not provide information regarding the cut-off value. In 3 studies [20, 22, 32], the same patient receives more than one volume expansion, and the final data analysis uses the data for each volume expansion. Two studies [20,23] evaluated preload responsiveness at two different period of surgery, so we divided the results of each study into two parts.

Results of meta-analysis

The Spearman correlation coefficient was 0.07 (*P* =0.00), indicates that although a significant threshold effect exists, the effect on the results is small. The Cochrane-Q value of the AUC was 39.175 (95% CI 0.79-0.85, *P* <0.001) and I2=95%, indicates significant heterogeneity exists. Because of the significant heterogeneity of the pooled results, we performed a further subgroup analysis based on the patient's condition. The results of the meta-analysis are described in Table 1 and Fig. 4. The pooled area under the receiver operating characteristic (AUC) to predict preload responsiveness in patients was 0.82 (95% confidence interval (CI) 0.79 - 0.85). The pooled sensitivity was 0.77 (95% CI 0.67-0.85) and the pooled specificity was 0.77 (95% CI 0.71-0.82). It is shown that the accuracy of PVI predicting preload reactivity is not as high as reported in previous meta-analyses[34-36]. Our new discovery is the result of patients without undergoing surgery (AUC=0.86, Youden index=0.65) was reliable.

The I2 value was 95%, indicating statistically significant heterogeneity. After performance of meta-regression, we found the choice of intravenous colloid injection as a means of preload responsiveness was a significant cause (*p* =0.02) of the heterogeneity; however, following the exclusion of the 17 studies which used intravenous colloid injection [10-16, 19-21, 23, 24, 29-33]， the heterogeneity remained significant（I2=84%）.

The sensitivity analysis showed that 2 [16, 27] of the studies may have contributed to the heterogeneity; however, following the exclusion of the two studies, the heterogeneity remained significant（I2=95%）.

Discussion

Applicable patients

The PVI has higher accuracy for mechanically ventilated patients with a regular rhythm and nonthoracotomy [39]. The PVI reflects the degree of change in PI caused by breathing over a period of time, so it is greatly affected by cardiopulmonary exercise. The PVI has ability to reliably predict preload responsiveness, provided that the pressure changes in the chest cavity are sufficiently obvious enough and the cardiopulmonary interaction between different respiratory cycles is stable. Therefore, the PVI and other dynamic parameters of cardiopulmonary interaction are more suitable for patients with mechanical ventilation rather than spontaneous breathing. The results of the meta-analysis also showed that PVI was less reliable in the subgroup of cardiac surgery (Youden index =0.45) than in the non-cardiac surgery subgroup (Youden index =0.49).

Heterogeneity

Significant heterogeneity exists in both the overall group and most of the subgroups, which may be because the patient’s conditions are complex, the surgical methods are different and the fluid management methods are different. Meta-regression showed that intravenous colloid injection selection may be the source of heterogeneity (*p*=0.02). However, with the exception of 17 studies [10-16, 19-21, 23, 24, 29-33] that employed intravenous colloid injection as a method of preload responsiveness, the heterogeneity remained significant (I2=84%). The sensitivity analysis showed that 2 [16, 27] of the studies may have contributed to the heterogeneity; however, following exclusion of the two studies, the heterogeneity remained significant（I2=95%）. The heterogeneity was relatively low in the subgroups undergoing noncardiac surgery(I2=63%), which may be because of the patients undergoing cardiac surgery are often non-sinus rhythms and have a greater impact on tissue perfusion. There was no significant heterogeneity in the subgroups of patients without undergoing surgery (I2=33%), which may be because certain surgical stimuli (such as pain) and procedures (such as liver surgery for inferior vena cava) may cause changes in vascular tension or hemodynamics. There was no significant heterogeneity in the crystalloid subgroup (I2=23%), potentially because of the small number of studies (n=4).

In general, the heterogeneity within each subgroup is stable. After quality assessment of the included studies, we believe that heterogeneity will not have a fundamental impact on the reliability of the meta-analysis result.

Perfusion situation

Under the monitoring of a pulse oximeter, the pulsating blood flow absorbs red and infrared light (AC), and the tissue and skin also absorb red and infrared light (DC). The ratio of the two parameter can calculate the PI :

$$PI=(AC-DC)\times 100\%$$

PVI reflects the degree of change in PI caused by breathing over a period of time. The formula is as follows:

$$PVI=[(PImax-PImin)/PImax]\times 100\%$$

Reliability of the PVI is largely affected by adequacy of perfusion [40]. Peripheral perfusion deficiency can result in impaired blood flow to a stable constant partly caused by skin and other factors that signal the volume in the tissue. To date, a pulsed oximeter, which is used to calculate the PVI, will not be able to determine whether the reduction of chest pressure is caused by the variety of cardiovascular system capacity or low perfusion of the monitored site, so any influence on peripheral perfusion factors, that is, the factors that affect PI, can affect the reliability of the PVI prediction of preload responsiveness [34]. The sensitivity of the subgroup of cardiac surgery is lower than that of the other subgroups and overall (0.67 95% CI 0.40-0.87). Broch O et al. [9] reported that the PVI reliably predicted preload responsiveness only in patients with high perfusion level (PI＞4%).

When using the PVI to guide goal-directed volume expansion, anesthetists should pay attention to factors that can affect perfusion situation of the monitored site (such as peripheral vascular disease, severe heart failure, application of vasoactive drugs, and damage of the monitored site).

Types of volume expansion

The results of the synthesis show that the subgroups with colloid injection (Youden index=0.59 AUC=0.83) are more reliable than the subgroups with crystalloid injection (Youden index=0.46 AUC=0.79). This may be because the colloidal fluid has a better effect on the macrocirculation and the microcirculation [41], thus increasing the reliability of the PVI.

The best cut-off value

The included results show that the PVI has a wide range of best cut-off value for defining responders to preload responsiveness, which range from 7% to 20%. The different conditions for each study (the patient’s underlying disease, volume stroke, age, type of surgery, in operating room or in ICU), and patients’ different fluid management (the application of vasoactive drugs, rate of intravenous infusion and type of volume expansion) may contribute to high variability.

Monitored site

The monitored site could affect the morphology and respiratory variation of the PVI[42-45]. Desgranges et al. [12] compared finger, forehead and ear as monitored site, reporting that the choice of three monitored sites has no significant impact on accuracy. While Hood et al. [19] reported that the PVIfinger can reliably predict increases in SV, while the PVIearlobe can not reliably predict increases in SV in dynamic intraoperative conditions. Fischer et al. [15] demonstrated PVIforehead was more accurate than PVIfinger in predicting preload responsiveness after cardiac surgery. For safety and convenience, the PVIfinger remains the preferred choice for most patients, with the PVIforehead and PVIearlobe as stable alternatives [12].

Limitations

Our systematic review has several limitations. First, significant heterogeneity exists in both the overall group and most subgroups; thus, differences between patients and surgeries should be considered in the application of the PVI. Second, we only included mechanically ventilated patients, which limited the results extrapolated to all patients. Studies on the monitoring of the PVI on patients with spontaneous breathing must be conducted. Third, subgroup analyses of the child subgroup and the passive leg raise subgroup were not performed because of insufficient studies. Fourth, the best cut-off value for the PVI varied within great ranges, and the best cut-off value for different types of patients and surgeries remains to be studied. Finally, although PVI is more reliable for patients in the ICU, most of these patients are also applying other more accurate invasive monitoring (such as arterial blood pressure monitoring), so PVI is more recommended as a replacement of pulse oxygen.

Conclusion

The PVI, as a noninvasive and automatic hemodynamic monitoring, has limited ability to predict the fluid responsiveness of mechanically ventilated patients, except patients without undergoing surgery and patients in ICU. The PVI can plays an important role in bedside monitoring for mechanically ventilated patients who are not undergoing surgery, such as patients after cardiac surgery and shock patients. Patients who are expanded with colloid and patients who undergoing cardiac surgery may be more suitable for PVI. For different individuals, the optimal PVI cut-off value must be further determined.

Abbreviations

PVI: Pleth Variability Index; PI: perfusion index; CI：confidence interval ；AUC: area under the curve; ICU: intensive care unit;

Declarations

Funding

No funding was received for this study.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

Tianyu Liu , Chao Xu and Dunyi Qi made substantial contributions to conception and design of the study; Min Wang and Zheng Niu searched literature, extracted data from the collected literature and analyzed the data; Tianyu Liu wrote the manuscript; Min Wang and Zheng Niu revised the manuscript; All authors approved the final version of the manuscript.

Addition material

Additional file 1

Additional file 1 Characteristics of the retrieved studies, including published year, setting, type and mean age of patients, sample size, type of fluid challenge and definition of responsiveness of included studies.

Additional file 2

Additional file 2 Results of the retrieved studies, including sample size, true positive, false positive, false negative, true negative, best cut-off value, sensitivity, specificity, AUC and r value of included studies.

Ethics approval and consent to participate Not applicable

Consent for publication Not applicable.

Competing interests

The authors declare that they have no competing interests

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Tables

Table 1: Clinical characteristics of the study cohort and stratified by conscious state at admission.

	Cohort n=180	VS n=123	MCS n=57	*p* *
Age (years)	51.1 ± 17.3	50.1 ± 16.4	53.1 ± 19.2	0.279
Male (%)	120 (66.7)	84 (68.3)	36 (63.2)	0.610
Etiology (%)				0.079
Traumatic	54 (30.0)	37 (30.1)	17 (29.8)	
Anoxic	24 (13.3)	21 (17.1)	3 (5.3)	
Vascular	102 (56.7)	65 (52.8)	37 (64.9)	
Days in ICU (%)				0.974
<31	71 (39.4)	49 (39.8)	22 (38.6)	
31-59	83 (46.1)	56 (45.5)	27 (47.4)	
60-89	26 (14.4)	18 (14.6)	8 (14.0)	
Feed Administration (%)				0.031
PO	7 (3.9)	5 (4.1)	2 (3.5)	
NGT	118 (65.6)	73 (59.3)	45 (78.9)	
PEG	55 (30.6)	45 (36.6)	10 (17.5)	
Tracheostomy (%)	164 (91.1)	117 (95.1)	47 (82.5)	0.013
CRS	6.0 (4.0-9.0)	5.00 (3.0-6.0)	11.0 (9.0-12.0)	<0.001
Follow-up (weeks)	6.8 ± 2.0	7.4 ± 1.4	5.6 ± 2.4	<0.001

** p-value referred to statistical comparison between VS Vs MCS groups.*

VS: Vegetate State; MCS: Minimal Conscious State; ICU: Intensive Cure Unit; PEG: percutaneous endoscopic gastrostomy; NGT: nasogastric tubes.

Table 2: Univariate and multivariate Fine-Gray models for the event emergence from altered consciousness state.

	Univariate		Multivariate †	
	HR (95% CI)	C Index	HR (95% CI)	C Index
Age (years)	1.01 (0.99-1.03)	0.313	1.00 (0.98-1.02)	
Male (vs female)	0.76 (0.41-1.42)	0.585	0.71 (0.36-1.38)	
MCS (vs VS)	9.36 (4.45-19.69) *	0.613	9.68 (4.46-21.01) *	0.708
CRS	1.36 (1.25-1.48) *	0.668	1.38 (1.26-1.52) *	0.699
Aetiology		0.554		
Anoxic (vs. Traumatic)	- §		-	
Vascular (vs. Traumatic)	1.25 (0.66-2.38)		1.00 (0.46-2.18)	
ICU days		0.588		
31-59 (vs <31)	0.82 (0.43-1.56)		0.56 (0.28-1.17)	
60-89 (vs <31)	0.43 (0.15-1.27)		0.36 (0.12-1.11)	
Tree Subgroups		0.604		
Subgroup B (vs A)	6.27 (0.61-842.86)			
Subgroup C (vs A)	10.33 (1.22-1346.99) *			
Subgroup D (vs A)	33.67 (4.57-4294.73) *			
Subgroup E (vs A)	81.77 (11.01-10442.44) *			

† Both multivariate models have been developed with covariates Age, Sex, Aetiology, ICU days and, alternatively, MCS/VS state or CRS value at admission.

**: p < 0.05; § p < 0.05 for the k-sample test comparing the subdistribution for the event emergence.*

HR: Hazard-Ratio; ICU: Intensive Care Unit; MCS: minimally consciousness state; *VS: Vegetative State; CRS: Coma-Recovery Scale*

Figures

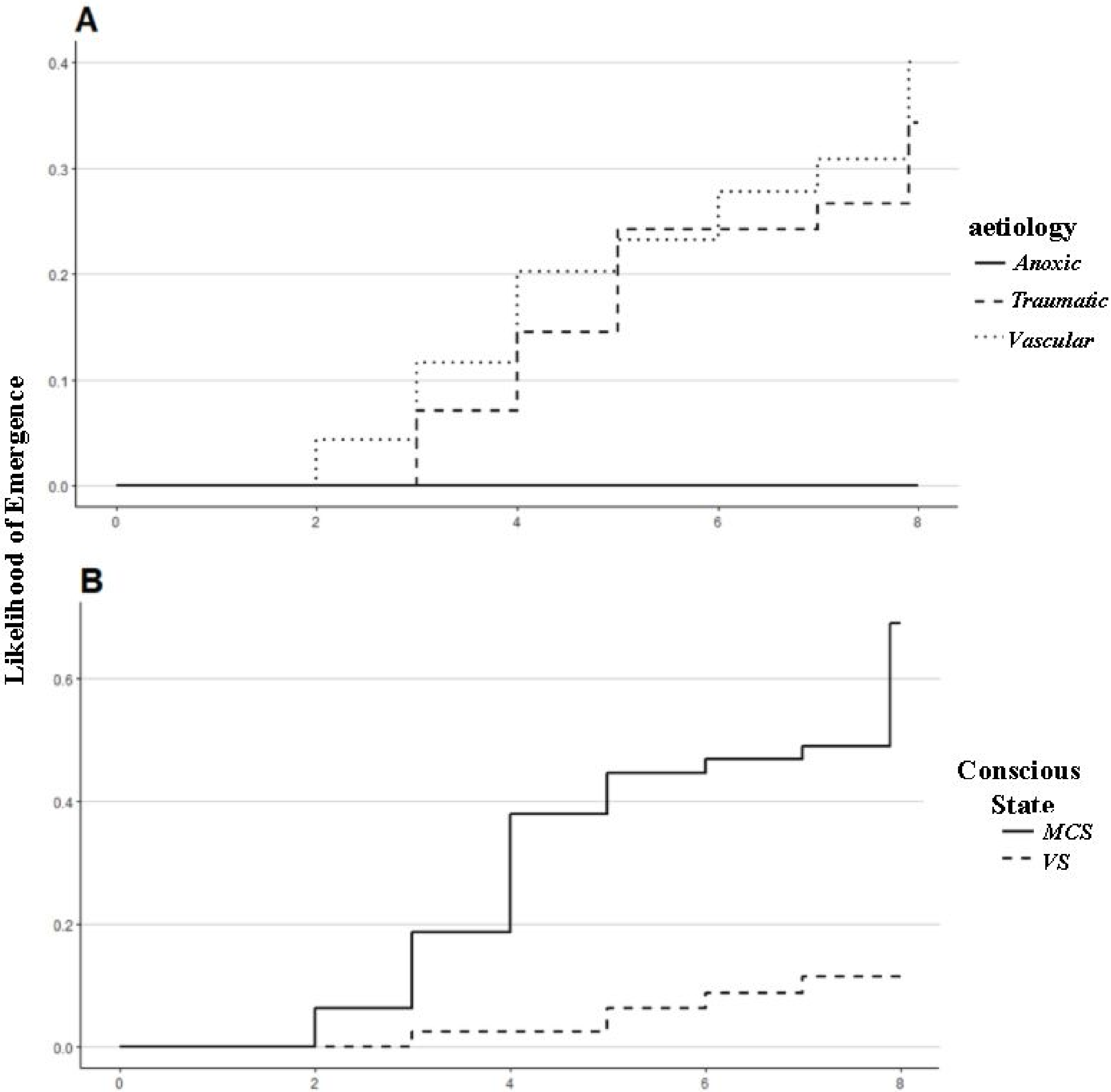

Figure 1

Likelihood of emergence measured with Coma Recovery Scale-Revised (CRS-R) by DoC aetiology and conscious state at admission.

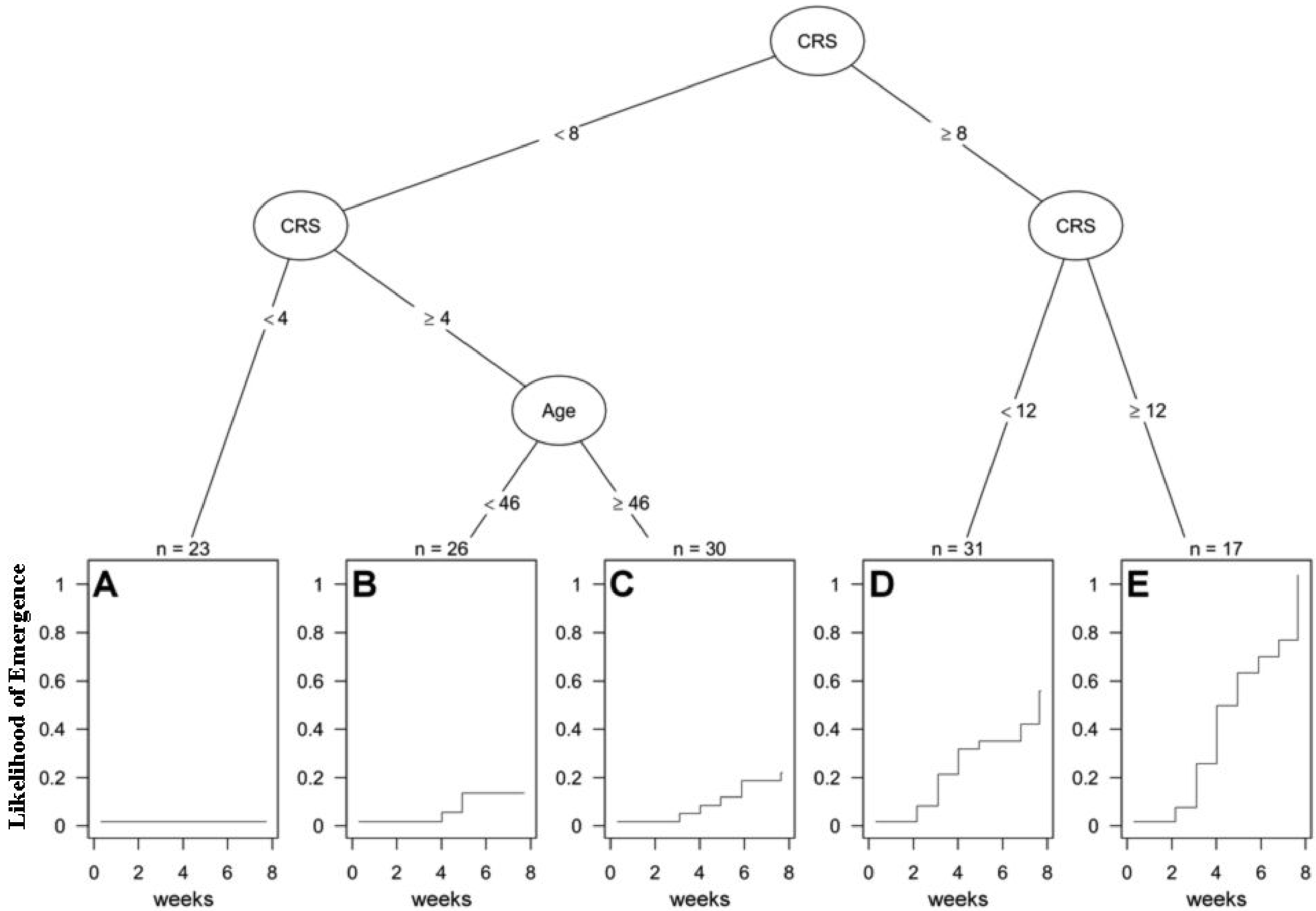

Figure 2

Survival tree for the event “Emergence” from DoC. Terminal panels show the cumulative incidence of Emergence of patients part of the subgroups defined by the conditions on the edges versus all other patients in the cohort.