Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is associated with cardiac injury and stroke severity in patients after acute stroke.

Mihalovič M., Mikulenka P., Línková H., Štětkářová I., Peisker T., Lauer D., Toušek P.

Cardiology and Neurology department, Third Faculty of Medicine, University Hospital Kralovske

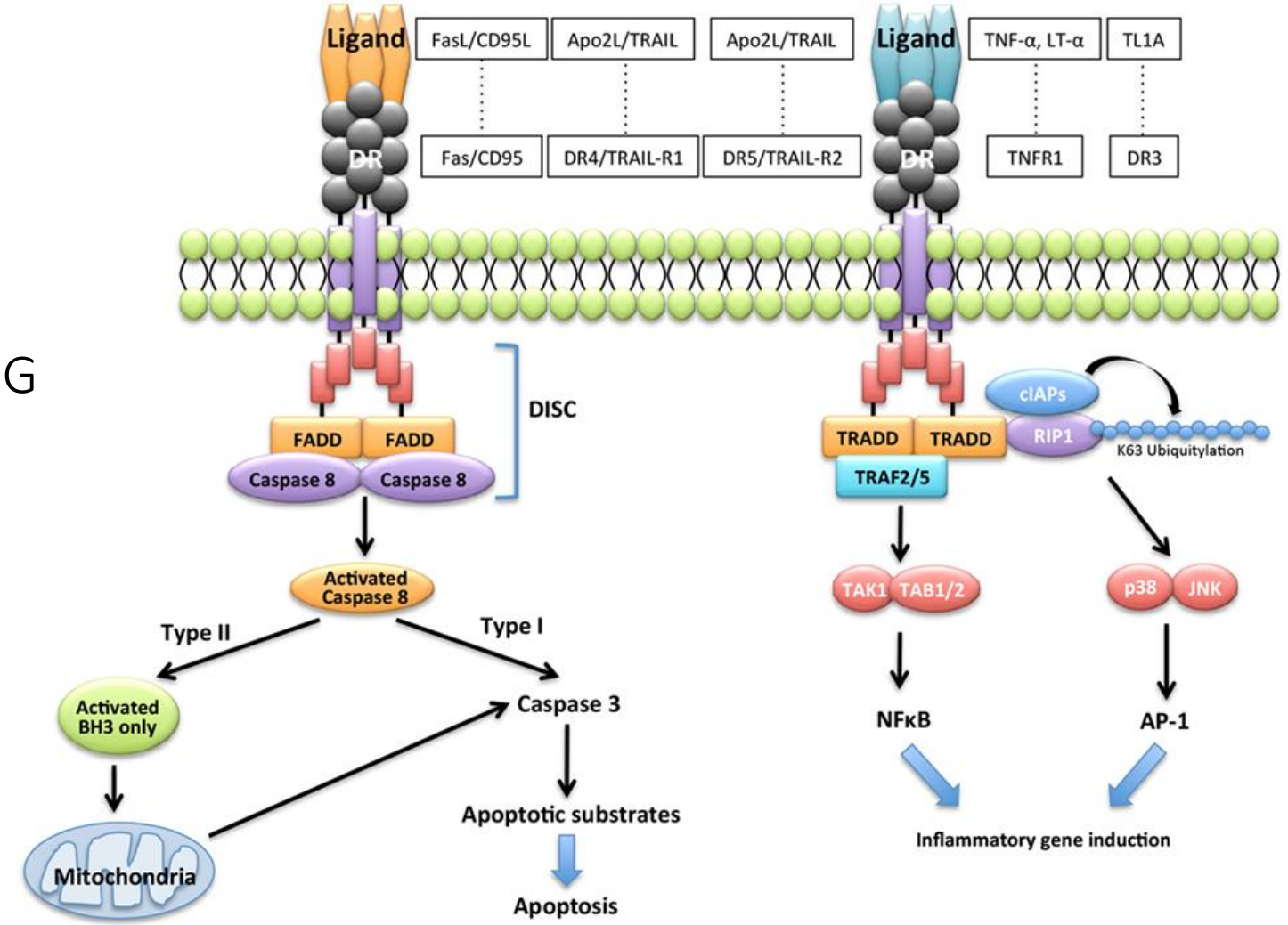
Vinohrady, Charles University, 100 34 Prague, Czech Republic.

Context

- Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is known to be associated with cardiovascular events.
- Objectives:
  - assess **TRAIL level dynamic changes** and its relation to stroke severity and its impact on the short-term outcomes
  - association with markers of cardiac injury

TRAIL

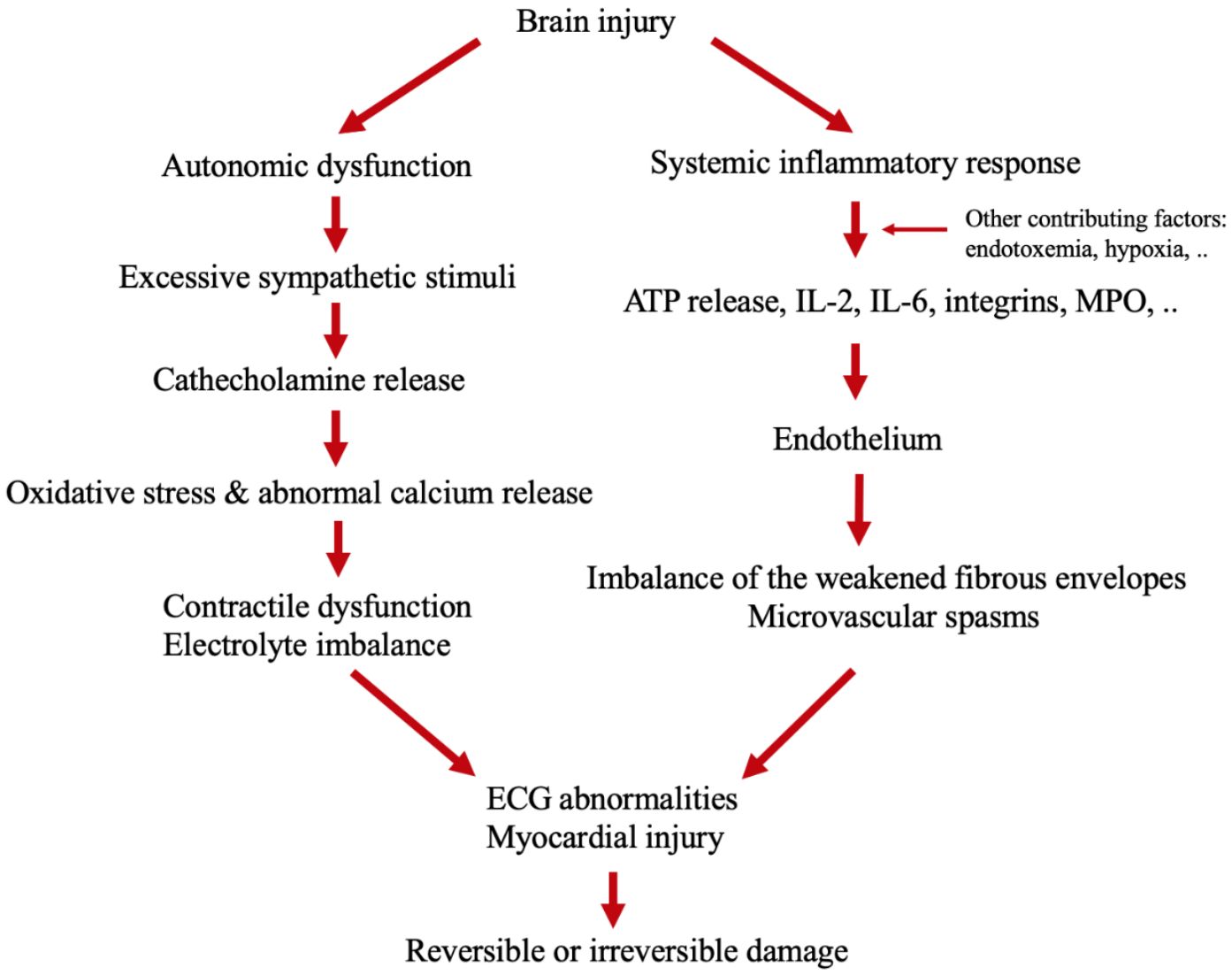
- TNF ligand superfamily
- Rec.: DR4, DR5, DcR1, DcR2, OPG
- potential predictor of poor prognosis in patients after AMI, with coronary artery disease (CAD)
- ANS, MMP2



Yamada, A., et al. (2017). "Dual Role of Fas/FasL-Mediated Signal in Peripheral Immune Tolerance"DOI: 10.3389/fimmu.2017.00403

Myocardial injury after stroke

- Autonomic dysfunction
  - HPA axis
- Immune response
- Other contributing factors



Mihalovic M., et al. (2021) „Myocardial injury after stroke“ DOI:10.3390/jcm11010002

Methods

Prospective single-center observational study

- 120 patients after acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH) were enrolled

Inclusion criteria

- age>18
- diagnosis of AIS or ICH within 48 hours of symptoms onset
- CT/MRI detected lesion
- informed consent

Exclusion criteria

- presence of hemodynamically severe valve defect
- heart failure with reduced ejection fraction
- impaired renal function (eGF<30ml/s)
- pregnancy

Laboratory analysis

- blood at the time of admission (day 0) and 24 ± 12 (day 1) and 48 ± 12 (day 2) hours later
- NT-proBNP, hs-cTnI, TRAIL
- blood samples – minerals, blood count, coagulation

Electrocardiogram analysis

- 12-lead ECG at admission, 24-, 48- hours and at release of the patient
- telemetry monitoring
- Holter/long term ECG monitoring

Echocardiography

- within first 5 days, left atrium size, ejection fraction, regional hypokinesis

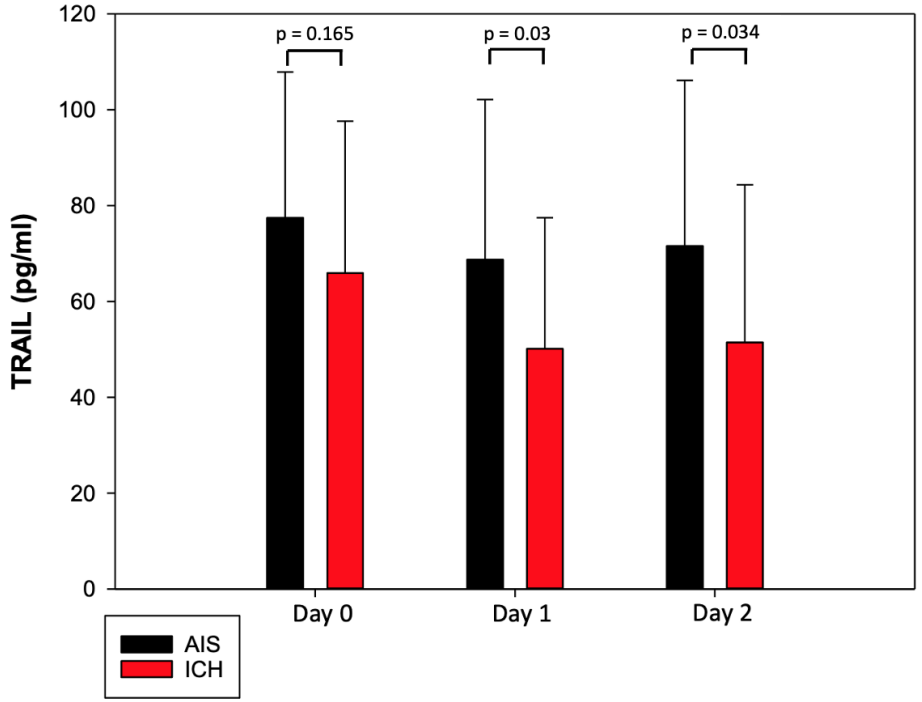
Statistics

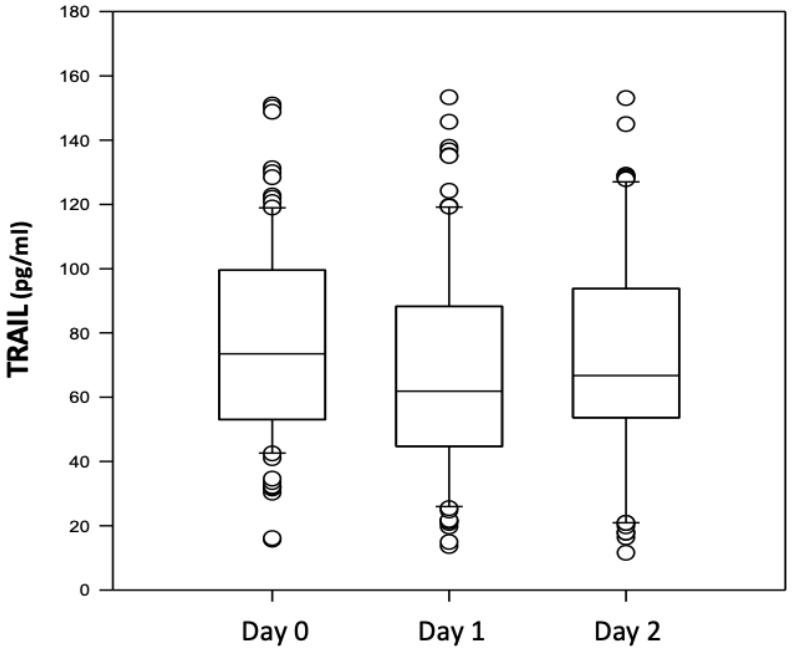
- Chi-square, Fishers exact test, regression analysis

Results - baseline

	Overall, n = 120	AIS, n = 104	ICH, n = 16	p Value
Age, Mean year (SD)	70.9 (12)	70.8 (11.8)	71.8 (13.5)	0.84
Male, n (%)	63 (52.5)	53 (51)	10 (62)	0.43
Arterial hypertension, n (%)	93 (77.5)	78 (75)	15 (93.7)	0.12
Smoking, n (%)	51 (42.5)	43 (41.3)	8 (50)	0.81
Dyslipidemia, n (%)	60 (50)	53 (51)	7 (44)	0.79
Diabetes mellitus, n (%)	29 (24.1)	24 (23.1)	5 (31.3)	0.53
Ischemic heart disease, n (%)	8 (6.7)	6 (5.8)	2 (12.5)	0.29
History of stroke/TIA, n (%)	13 (10.8)	10 (9.6)	3 (18.8)	0.38
Atrial fibrillation, n (%)	26 (21.7)	23 (22.1)	3 (18.8)	0.21
Renal insufficiency, n (%)	9 (7.5)	6 (5.8)	3 (18.8)	0.09
History of myocardial infarction, n (%)	4 (3.3)	3 (2.9)	1 (6.3)	0.44
NIHSS				
0 (No stroke symptoms)		0		
1–4 (Minor)		30 (28.8)		
5–15 (Moderate)		52 (50)		
16–20 (Moderate to severe)		16 (15.4)		
21–42 (Severe)		6 (5.8)		
mRS 90 days				0.02
0 (No symptoms) (%)		34 (34.7)	1 (6.3)	
1 (No disability despite symptoms) (%)		22 (22.5)	1 (6.3)	
2 (Slight disability) (%)		12 (12.2)	1 (6.3)	
3 (Moderate disability) (%)		6 (6.1)	1 (6.3)	
4 (Moderate severe disability) (%)		6 (6.1)	1 (6.3)	
5 (Severe disability) (%)		5 (5.1)	1 (6.3)	
6 (Dead) (%)		13 (13.3)	8 (57.1)	

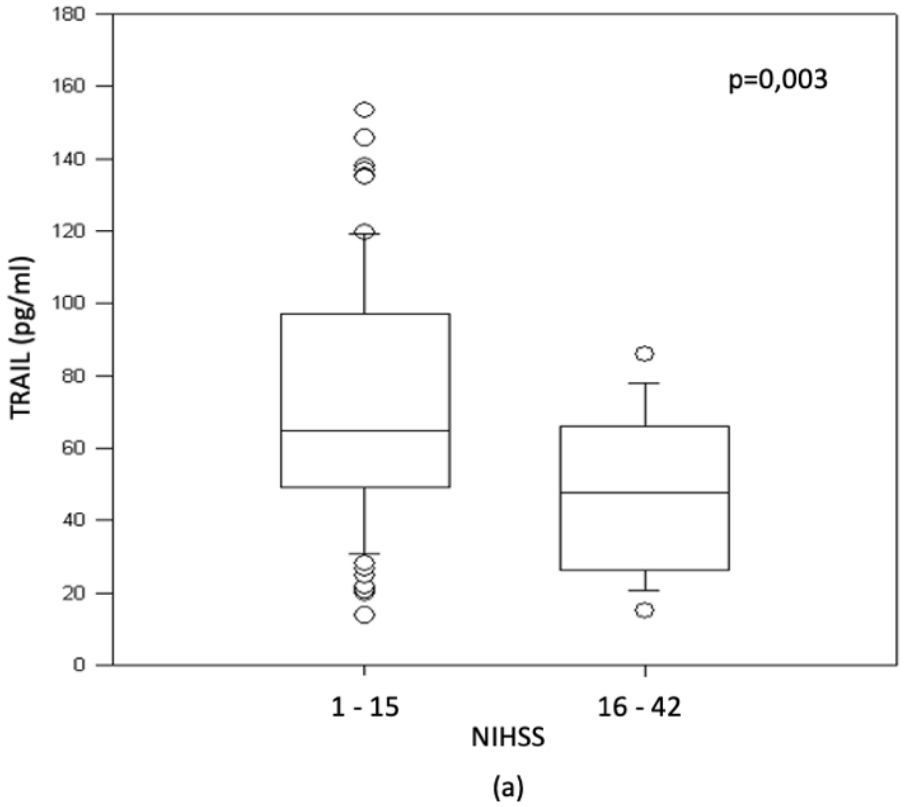
Differences between AIS and ICH group



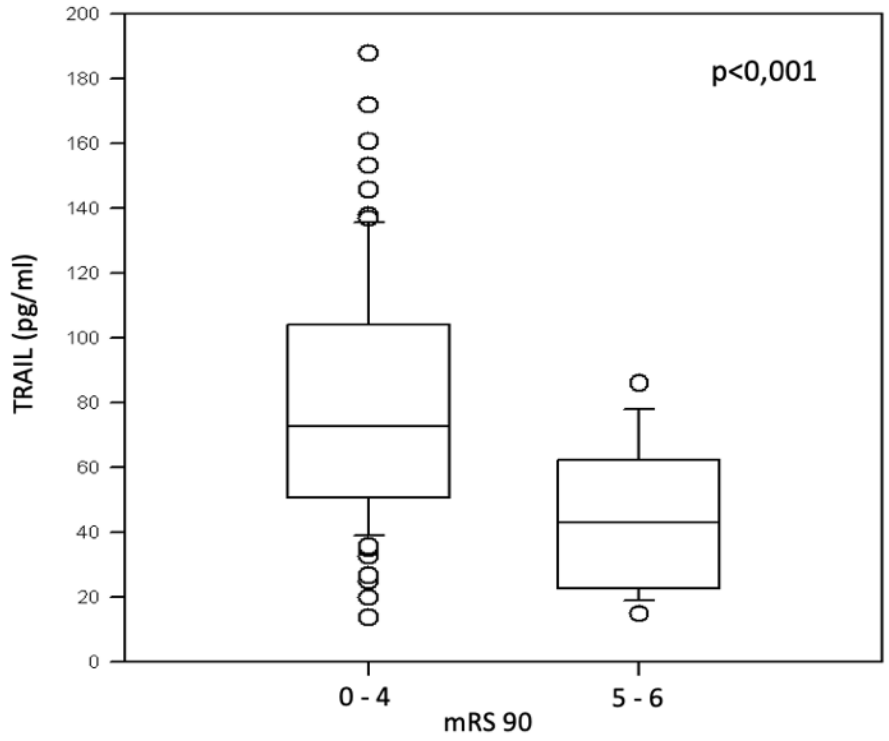


- Mean TRAIL level: *72.6pg/mL* in the AIS group and *55.83pg/mL* in the ICH group. Cut-off *64pg/ml*.
- We observed the lowest TRAIL level in both groups on day 1 with the mean level of *68.73 ± 33.42* in the AIS group and *50.12 ± 27.35 pg/m*L in the ICH group.
- TRAIL level was lower in the ICH group; we observed differences between TRAIL in the AIS group and the ICH group on day 1 (p = 0.03) and day 2 (p = 0.034).

Lower TRAIL association with stroke severity and short-term outcome



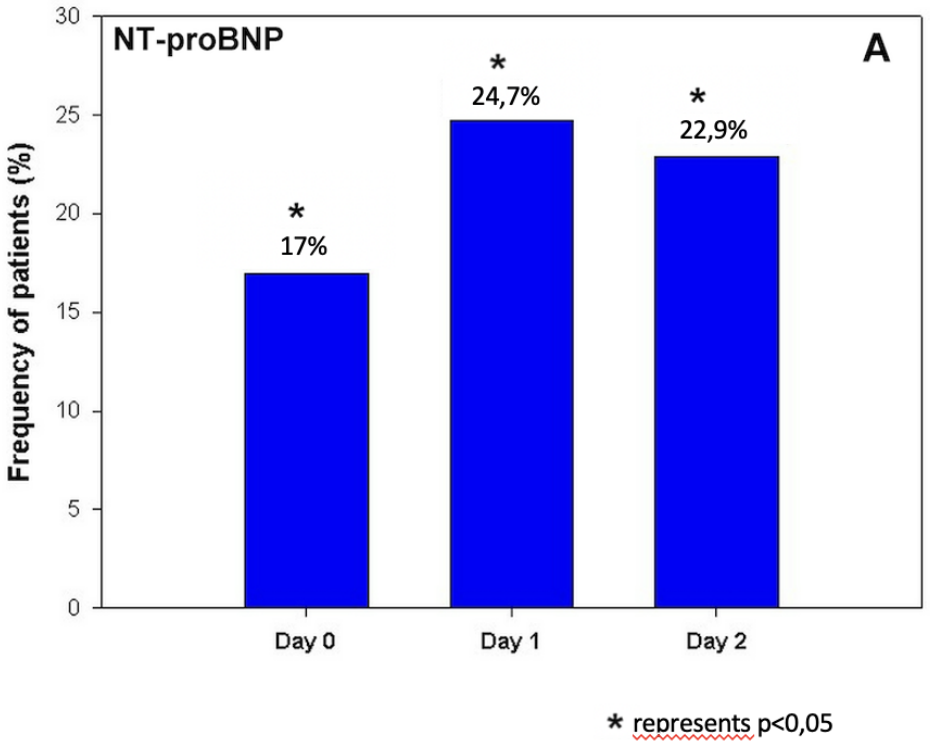
(a)



(b)

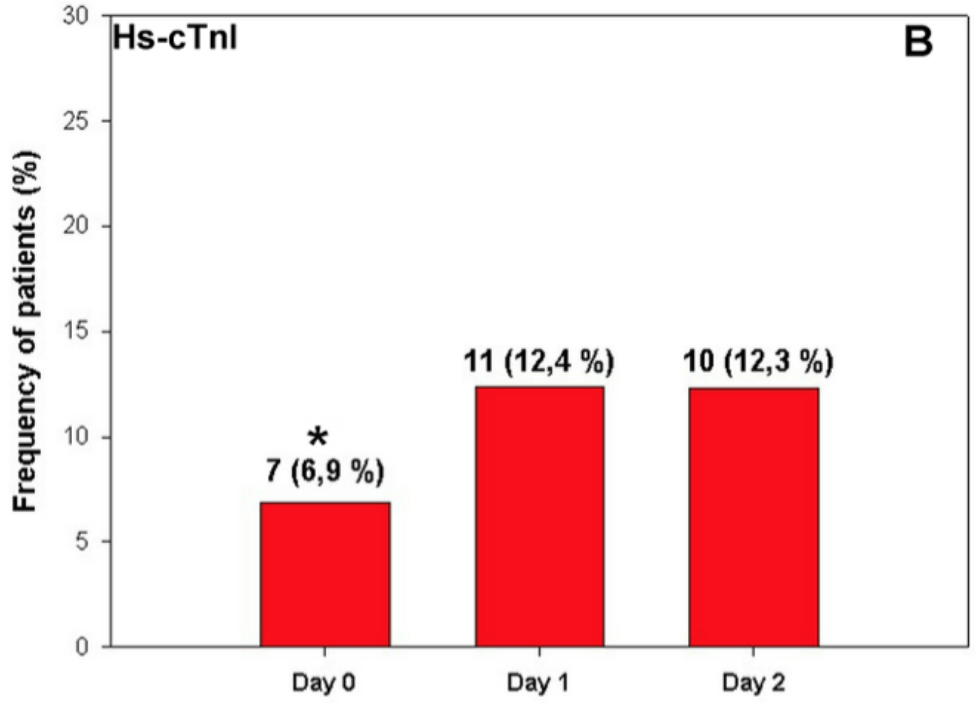
- moderate to severe stroke presented with lower TRAIL levels (*73.1 pg/mL* vs. *51.3 pg/mL*, $p = 0.003$)
- patients with worse functional outcome or death (mRS 90 5–6) presented with lower TRAIL levels (*72.6 pg/mL* vs. *43.1 pg/mL*, $p < 0.001$)

Relationship between TRAIL and NT-proBNP in patients after AIS



- 44.2% of the patients in the AIS group and 50% in the ICH group presented with elevated NT-proBNP >125 pg/mL during the first 48 h of hospitalization
- lower TRAIL level was associated with elevated NT-proBNP at the time of admission (p = 0.039), after 24 h (p = 0.043) and after 48 h (p = 0.023)

Relationship between TRAIL and hs-cTnI in patients after AIS



- Elevated hs-cTnI: AIS 22,1%, ICH 12,5%
- Lower TRAIL level was associated with hs-cTnI at admission (p=0,04)

Morphological, conduction and rhythm abnormalities

	N (%)	p Value
Arrythmias		
Atrial fibrillation	20 (21.3%)	0.13
AV block I.degree	8 (8.5%)	0.78
PVC	7 (7.4%)	*0.04*
LAH	4 (4.3%)	0.49
RBBB	4 (4.3%)	0.37
Sinus tachycardia	3 (3.2%)	0.75
Morphological changes		
QTc prolongation	16 (17.0%)	*0.052*
ST segment depression	11 (11.7%)	0.29
T wave inversion	10 (10.6%)	0.14
Flat T wave	6 (6.4%)	0.92
U wave	2 (2.1%)	0.89

Echocardiography

Acute ischaemic stroke

- 89/104 had echo exam
- 4 patients new LV regional dysfunction

Age	hs-TnI	NT-proBNP	TRAIL	Etio	NIHSS	Dg
68	52..325..1328	358..515..928	*63..33..19*	ICH		TTS
75	2430..10909..5681	353..487..571	*30..21..17*	iCMP	5	NSTEMI
75	1239..15557..1250	136..84..69	*16..26..17*	iCMP	8	NSTEMI
92	510..570..207	258..511..471	*32..15..20*	iCMP	23	TTS

Discussion and limitation

- Discussion - consumption
  - anti-inflammatory effects
  - autonomic dysregulation
  - reduction of inhibition power against apoptosis
- Limitations
  - acute phase
  - heterogenous regarding type of reperfusion therapy
  - ECG monitoring depended on the clinical condition of the patients
  - low number of pts

Conclusion

- Lower TRAIL is associated with stroke severity, unfavorable functional outcome, and short-term mortality in patients after acute ischemic stroke.
- Moreover, we described the association with markers of cardiac injury and ECG changes