

XXX. KONGRES NEMOCNIČNÉHO LEKÁRENSTVA



EUROPEAN UNION
European Regional Development Fund
OP Integrated Infrastructure 2014 – 2020

MINISTRY
OF EDUCATION, SCIENCE,
RESEARCH AND SPORT
OF THE SLOVAK REPUBLIC

SEKCIA
NEMOCNIČNÝCH
LEKÁRNIKOV

Farmaceutická starostlivosť pre špecifické skupiny pacientov

13. - 14.10.2022, Falkensteiner Hotel Bratislava****

Slovenskej lekárskej komory

Prognostické markery závažnej formy ochorenia COVID-19

Markusková L., Javorová Rihová Z., Martinkovičová A., Rábarová D., Sol'avová M., Dingová D., Paul Hrabovská A.

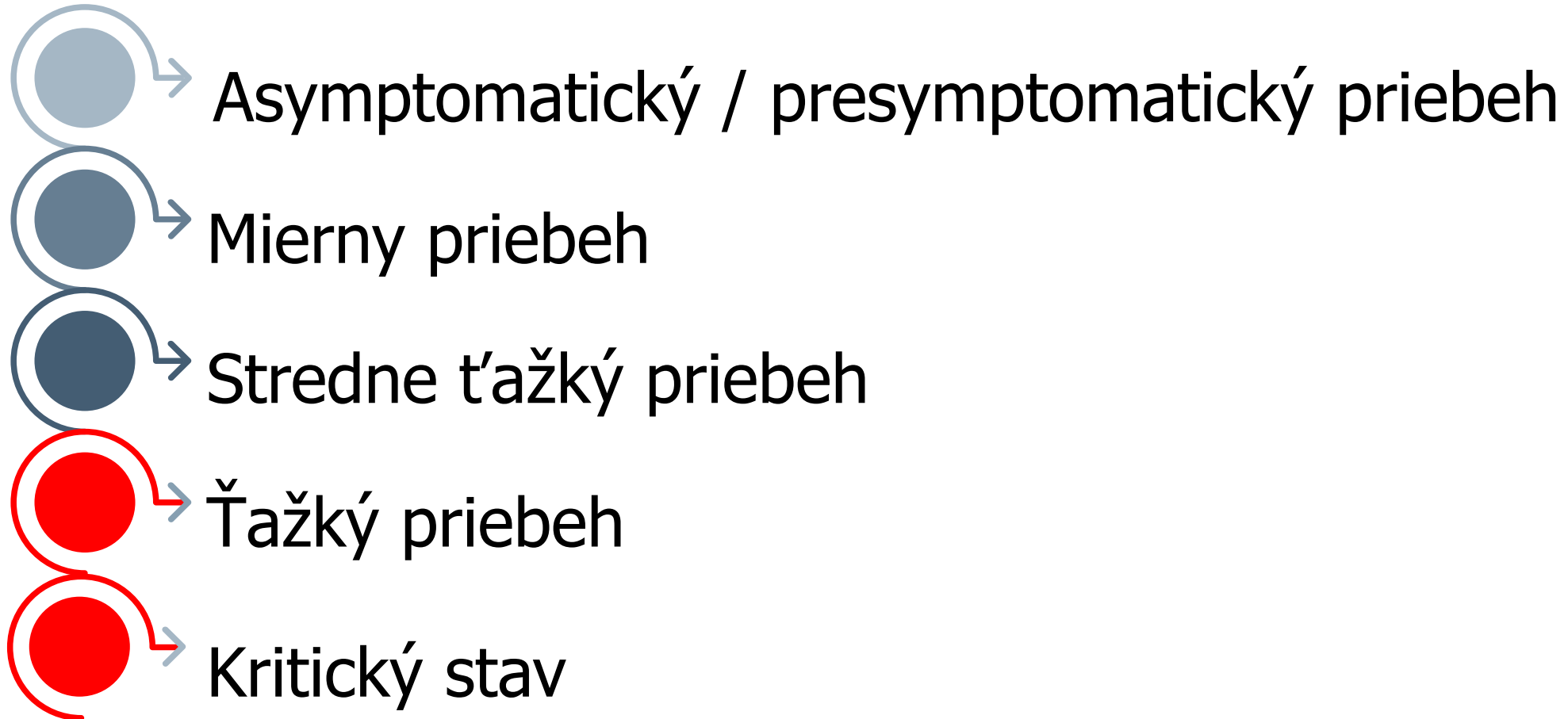


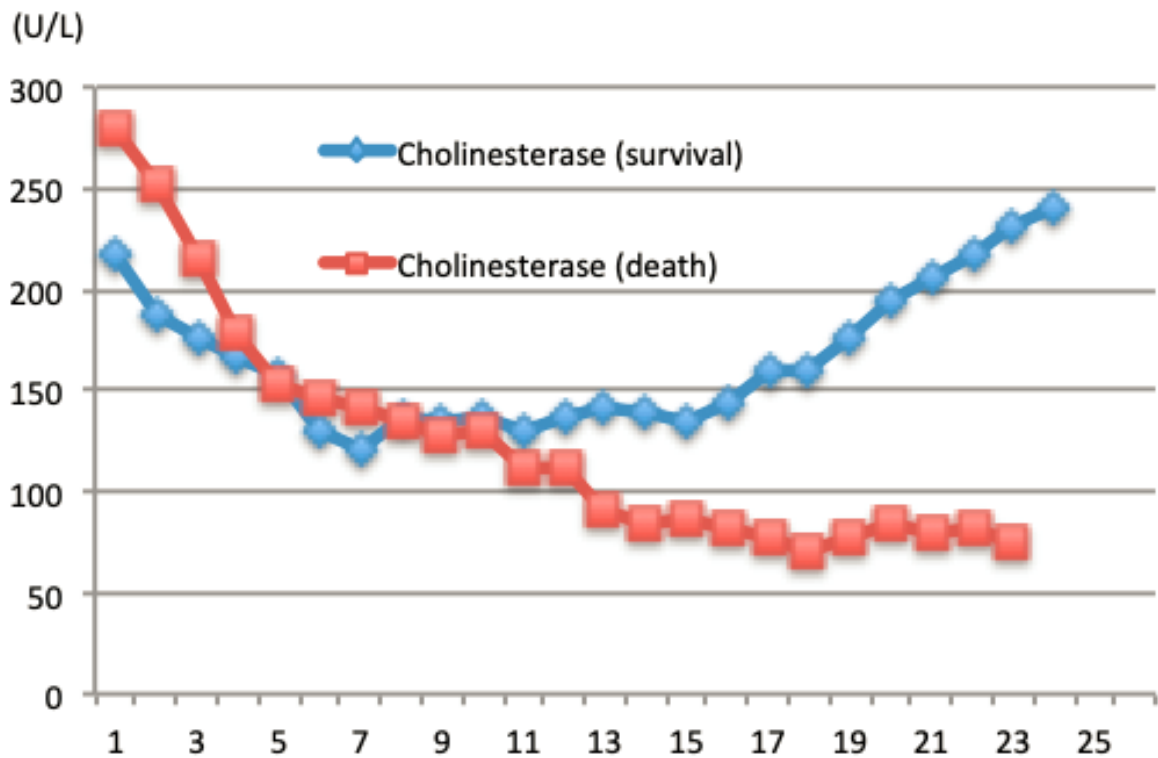
FARMACEUTICKÁ FAKULTA
Univerzita Komenského
v Bratislave

FAKULTNÁ NEMOCNICA
TRNAVA



COVID-19 podľa závažnosti klinických prejavov





Mild-to-moderate cases* (n = 11)	Severe cases** (n = 15)	p-value
Median (interquartile range)/frequency (%)	Median (interquartile range)/frequency (%)	
326 (228–394)	218 (185–279)	0.006

ChE (U/L)

Nakajima K (2021)



P V Prasad

Hans News Service | 8 May 2021 11:35 PM IST



A view of grocery store at SH Pet area in Nellore

HIGHLIGHTS

Though it sounds odd, Vsyas, the predominant trading community, are suspected to be highly vulnerable to the coronavirus pandemic.

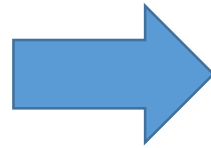
Nellore: Though it sounds odd, Vsyas, the predominant trading community, are suspected to be highly vulnerable to the Covid-19 pandemic.

Medical experts say that the mortality rate among them is very high and the pandemic has turned out to be terrible for a majority section of the community possibly due to their pre-existing genetic disorders. "Researchers must investigate such cases for discovering the basic reason behind the problem," say the members of the community.

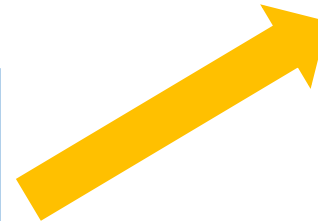


Môže byť BChE prognostickým markerom COVID-19?

FNTT
KAIM a KI

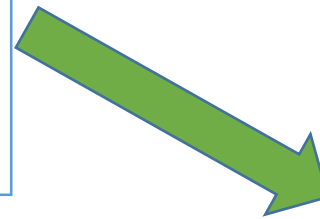
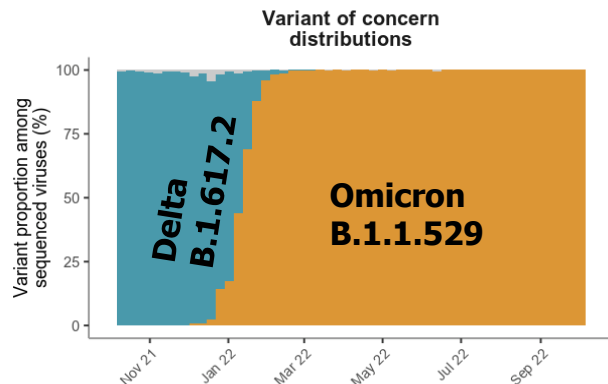


N = 148
(dg. U07.1)
♂ 83 ♀ 65
65r (26 - 96)



- Biochemické a imunologické markery
- Komorbidity
- Klinický stav
- Farmakoterapia

15/10/2021 – 31/5/2022



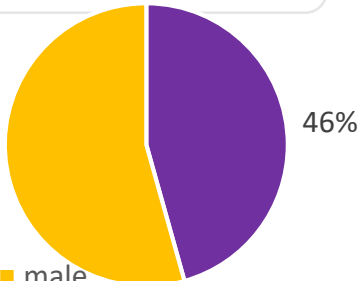
Aktivita BChE

Projekt schválený EK FaFUK a FNTT

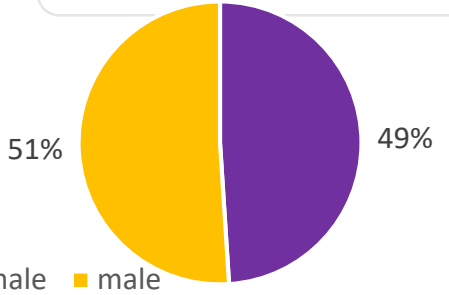


n = 148

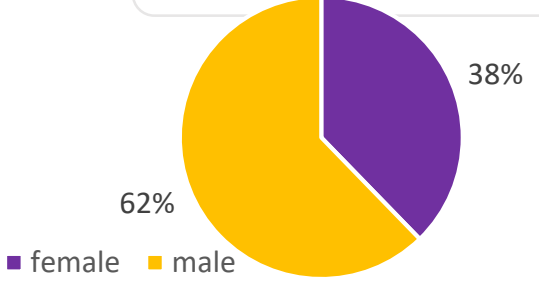
Prepustení
n = 46 (31 %)



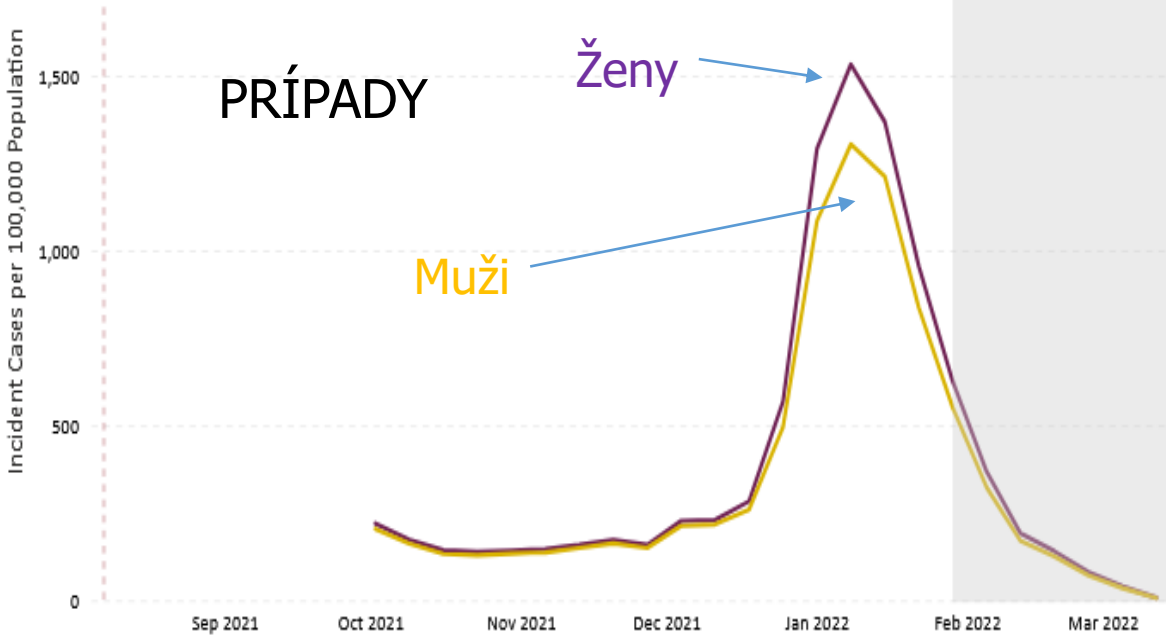
Preložení
n = 49 (33 %)



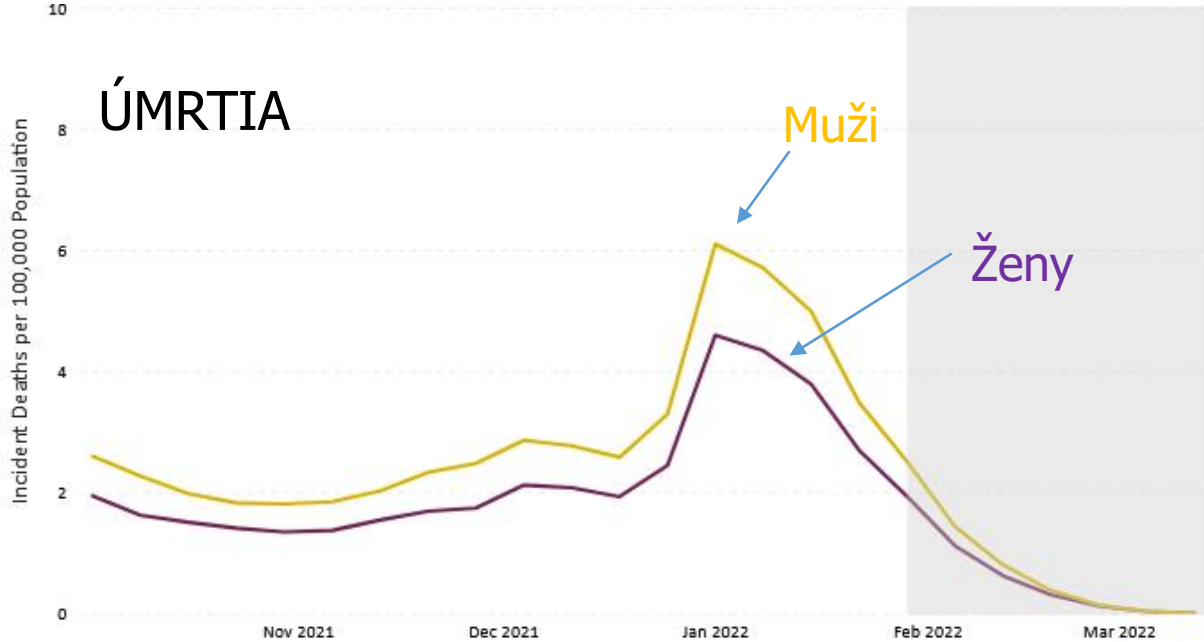
Nepreživší
n = 53 (36 %)



PRÍPADY



ÚMRTIA



Zdroj: NIH, CDC, ECDC, WHO

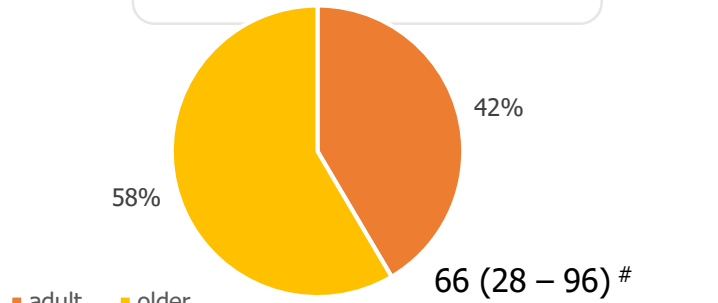
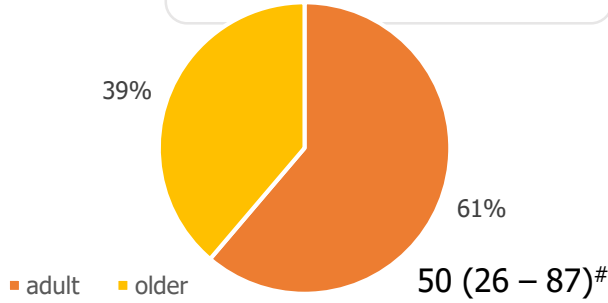
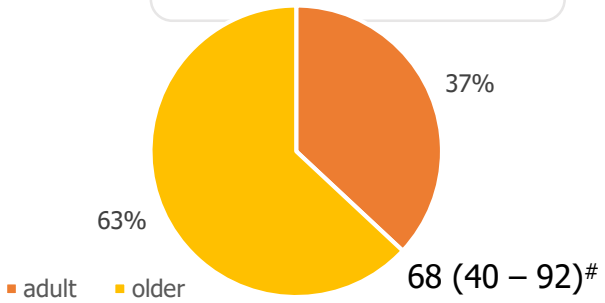


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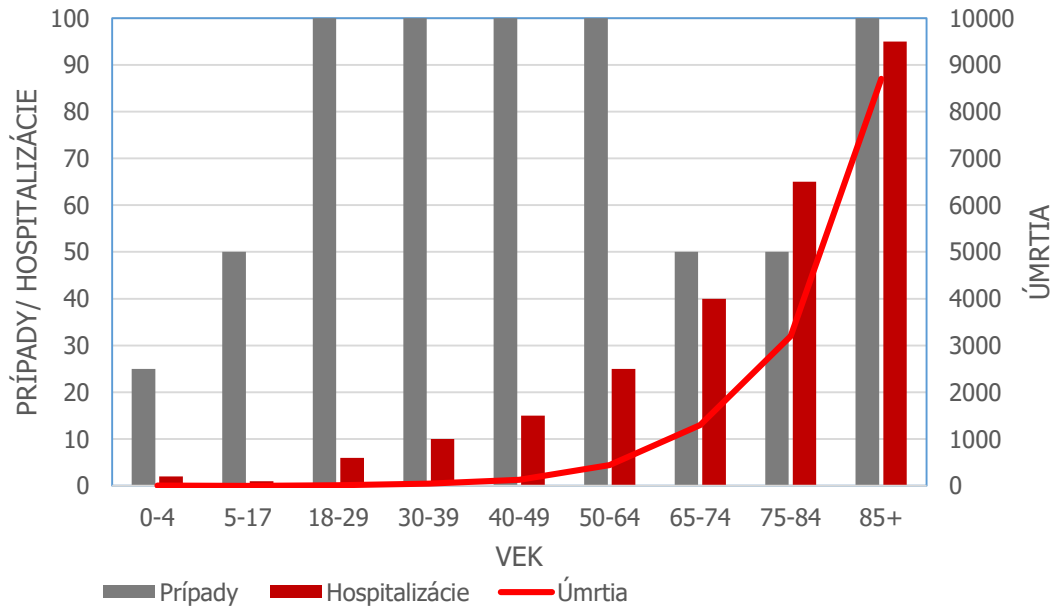
Prepustení
n = 46 (31 %)

Preložení
n = 49 (33 %)

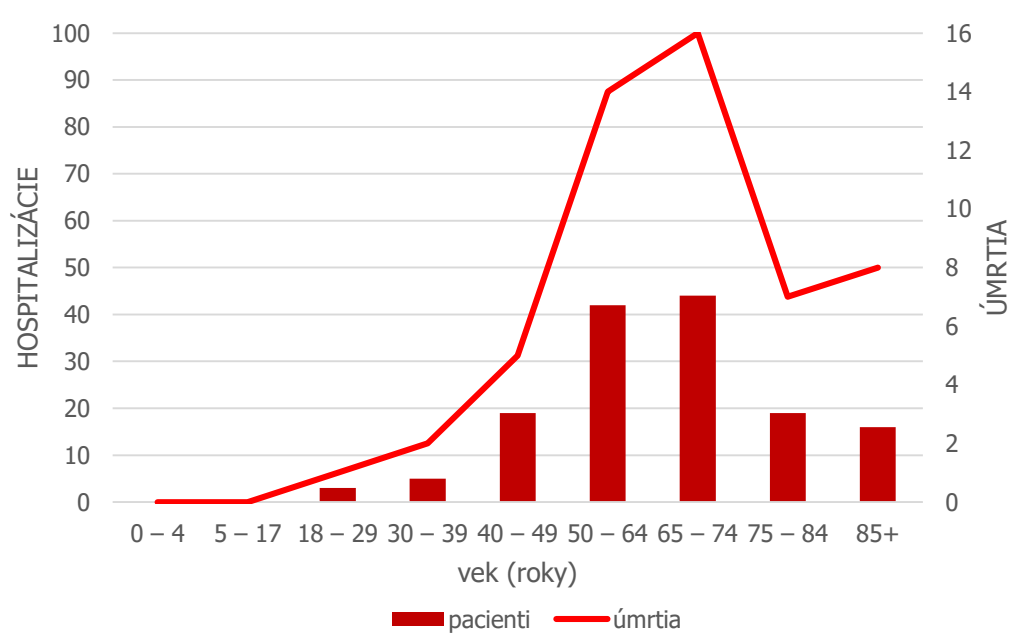
Nepreživší
n = 53 (36 %)

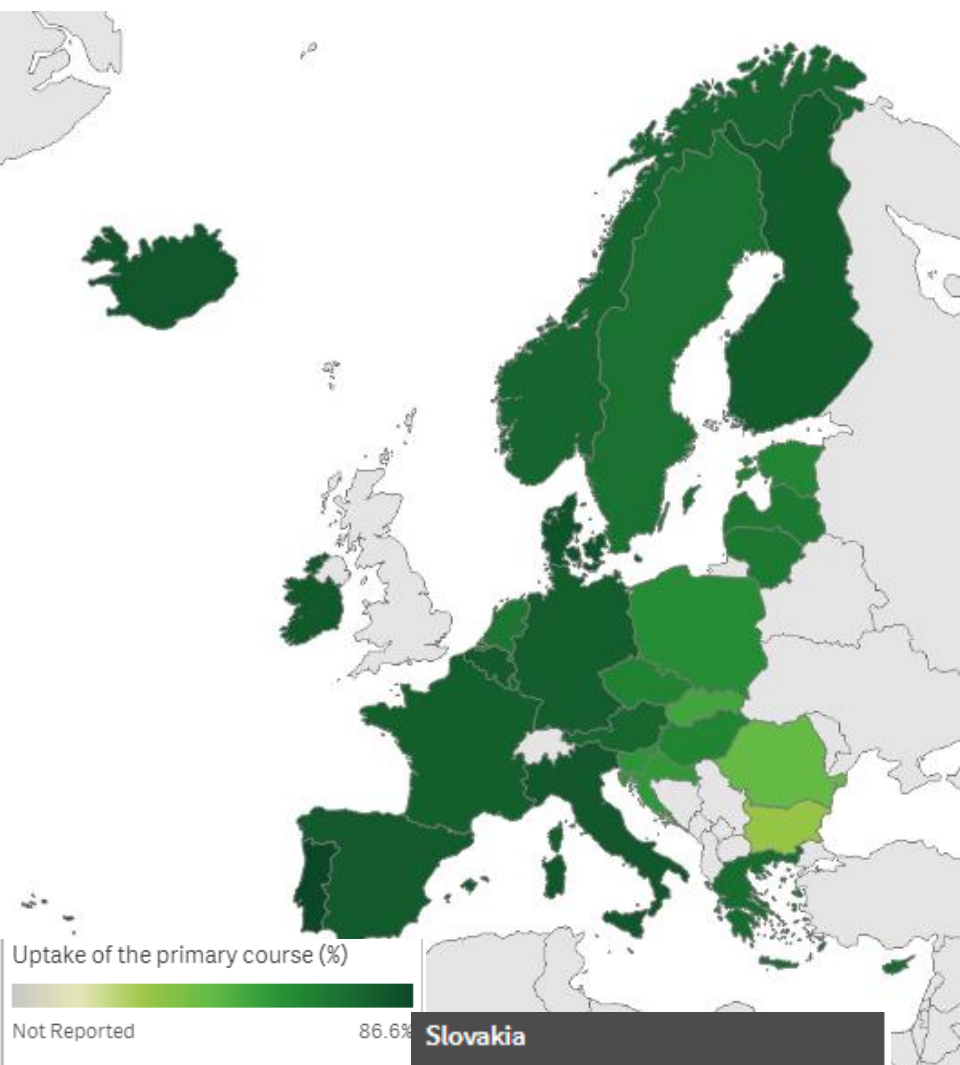


#median (min – max)

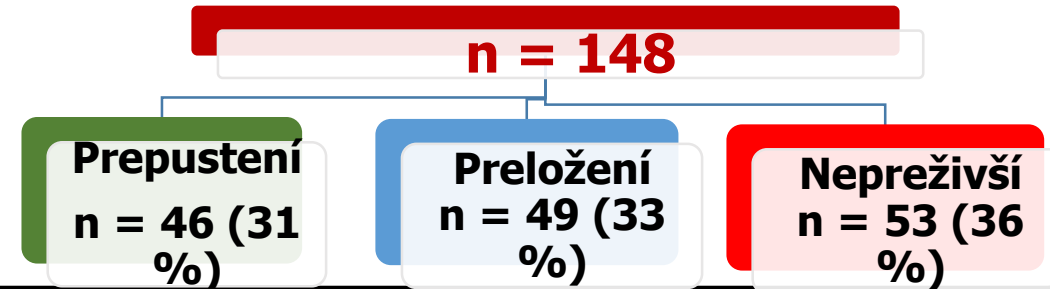



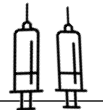
Na základe dát CDC

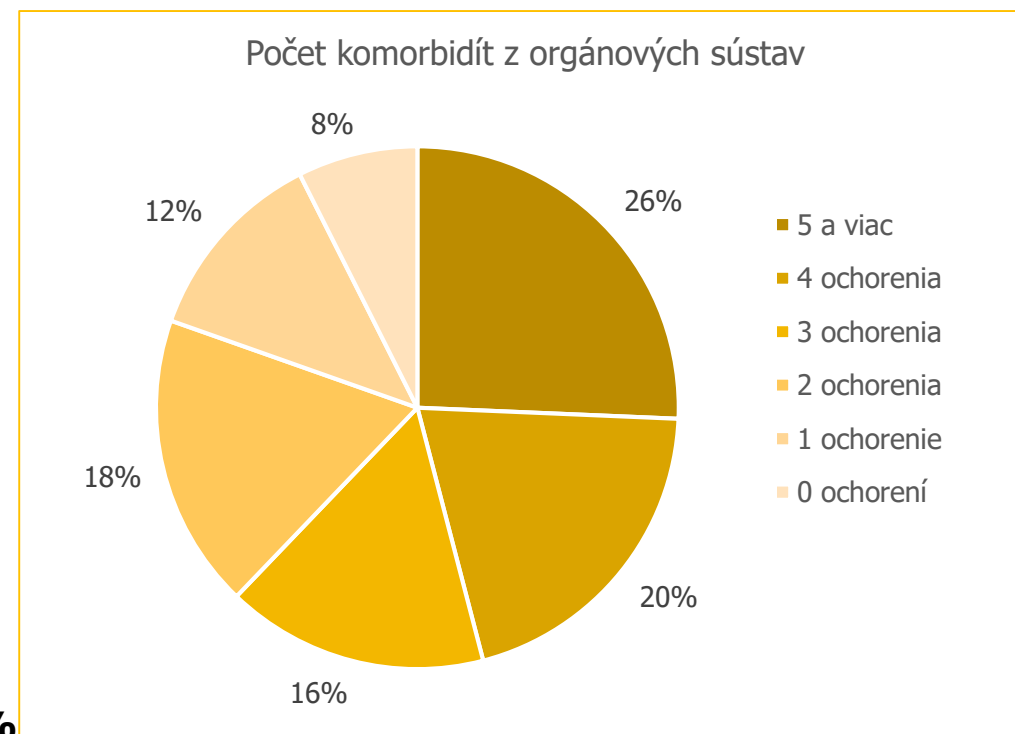
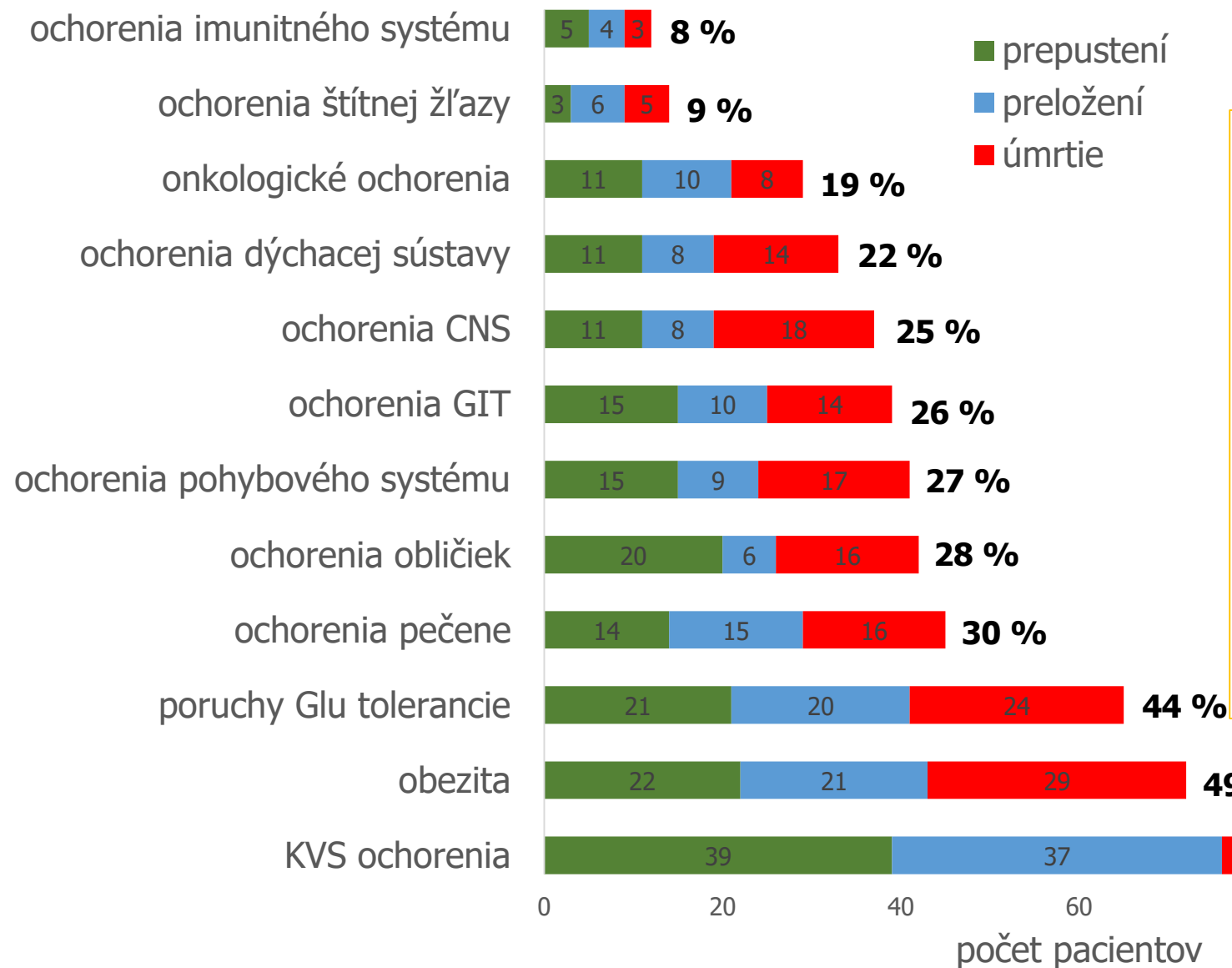




Slovakia	
Uptake at least one dose :	52.0%
Uptake of the primary course :	51.1%
Uptake of first booster :	30.8%
Uptake of second booster :	0.5%

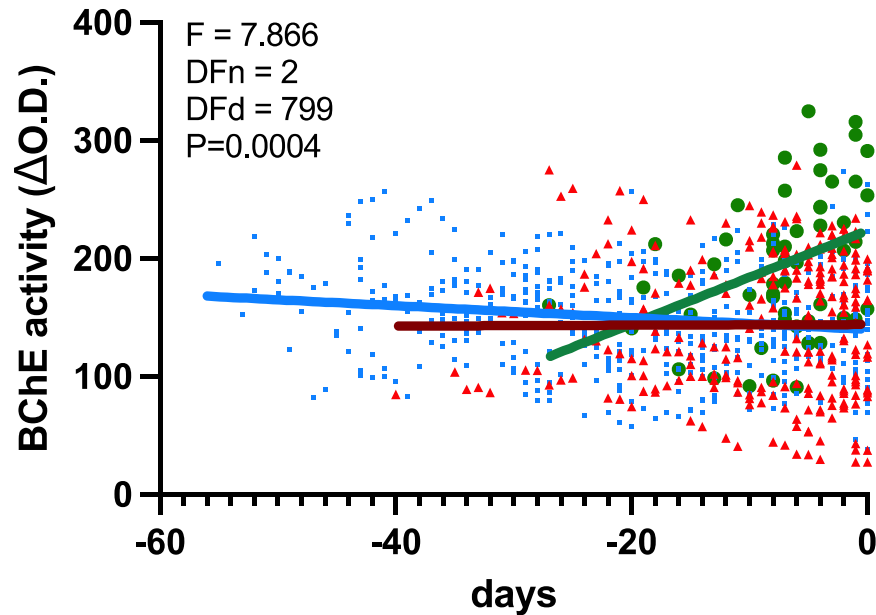


Očkovací status	n = 148	↑	→	↓
X	99 (67 %)	34 (34 %)	28 (28 %)	37 (37 %)
	5 (3 %)	1 (20 %)	3 (60 %)	1 (20 %)
	25 (17 %)	10 (40 %)	9 (36 %)	6 (24 %)
?	19 (13 %)	1 (5 %)	9 (47 %)	9 (47 %)



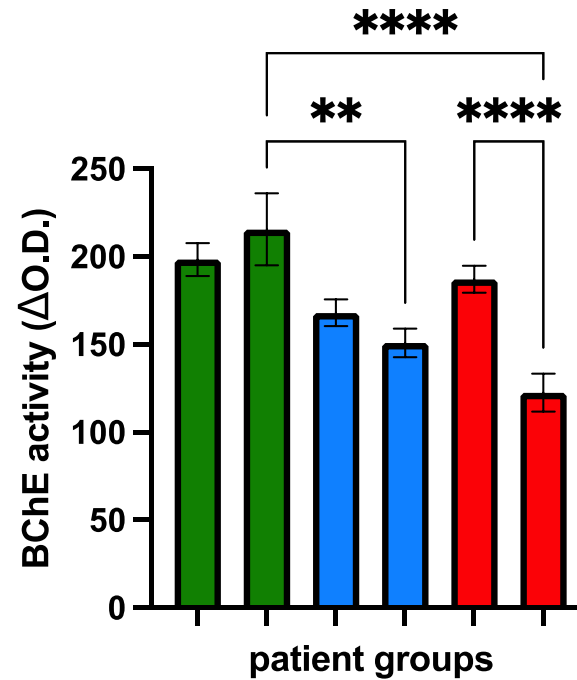
Môže byť BChE prognostickým markerom COVID-19?

Všetky namerané hodnoty aktivít sérovej BChE

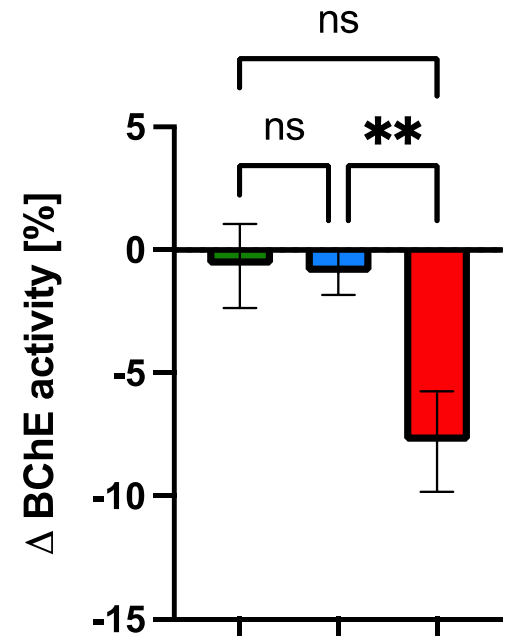


■ discharged ■ transferred ■ death

Zmeny v aktivite sérovej BChE na začiatku a na konci hospitalizácie

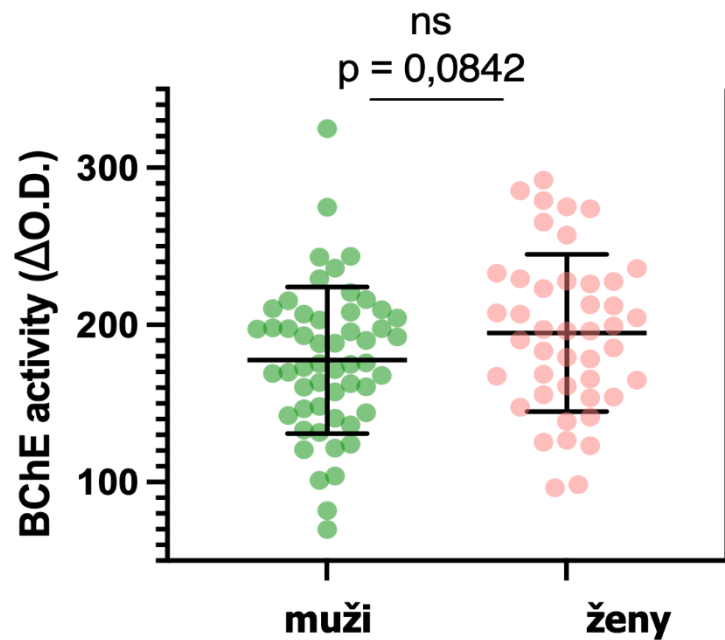


% zmeny aktivity sérovej BChE

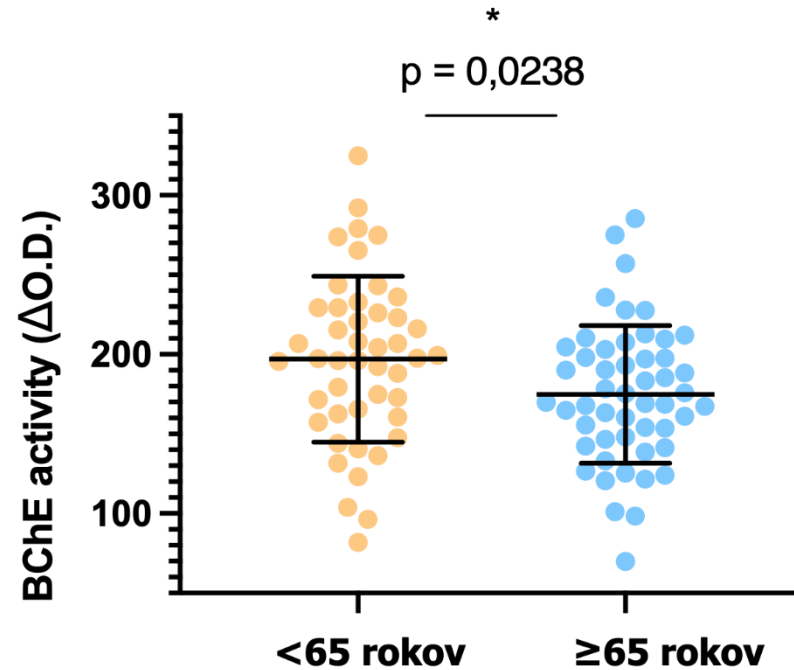


Môže byť BChE prognostickým markerom COVID-19?

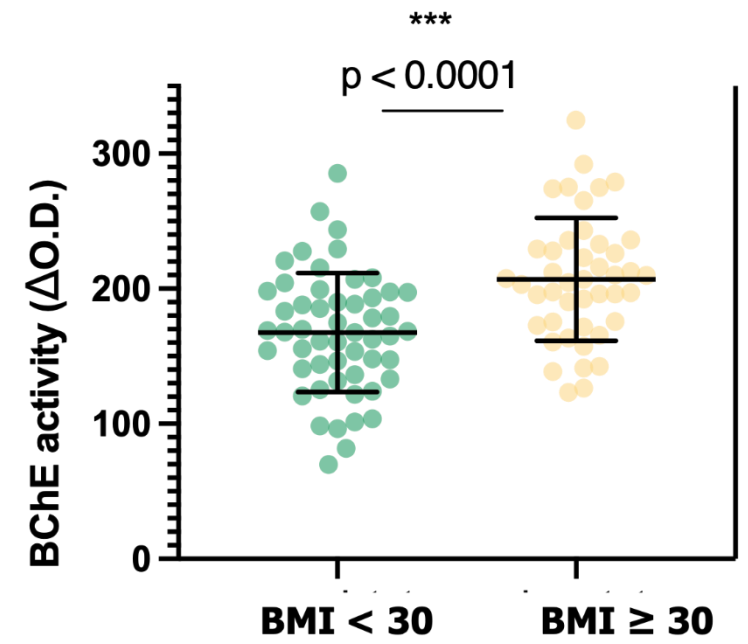
POHLAVIE ❌



VEK ✔️



BMI ✔️



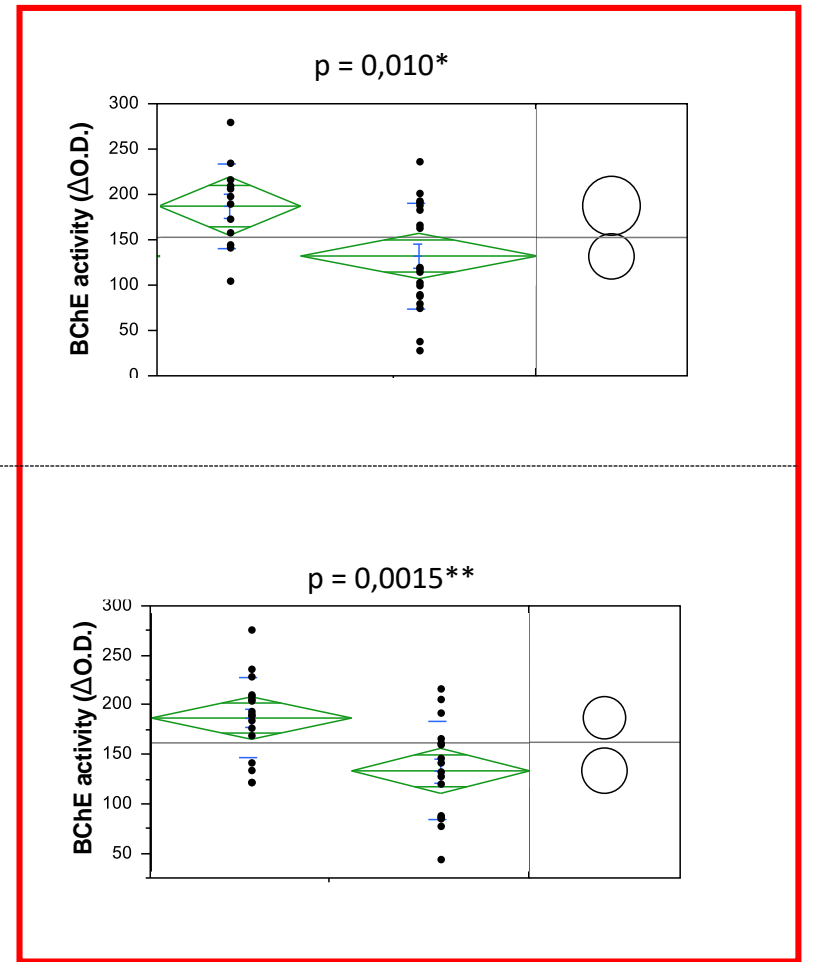
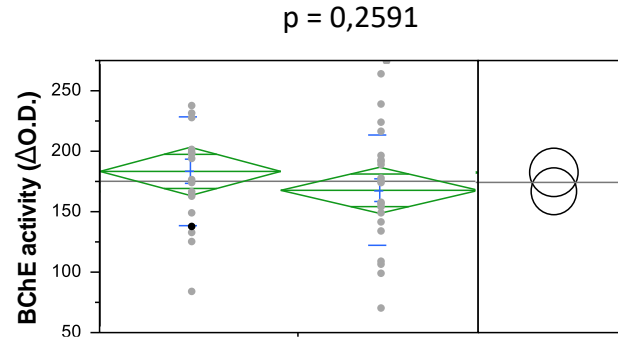
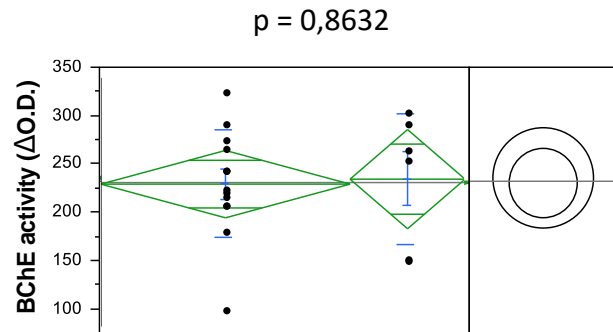
Môže byť BChE prognostickým markerom COVID-19?

PREPUSTENÍ

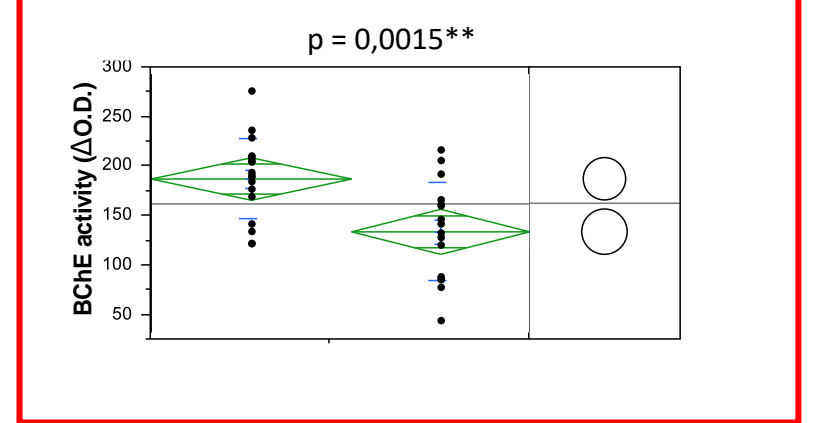
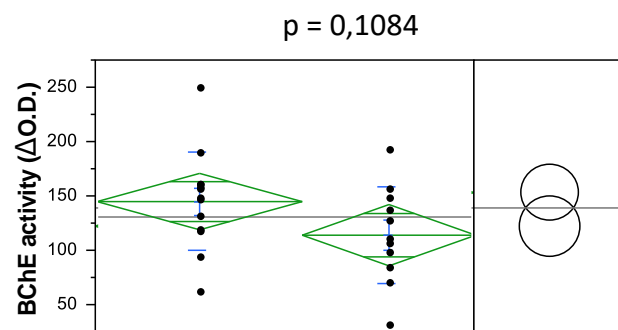
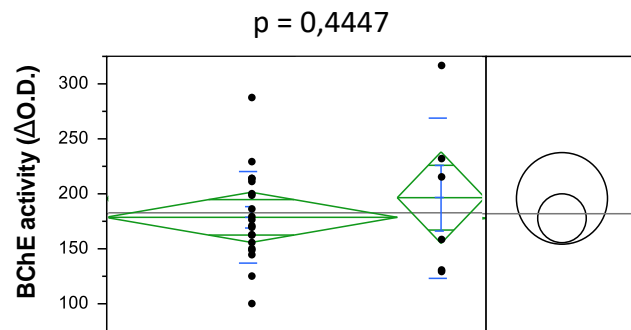
PRELOŽENÍ

NEPREŽIVŠÍ

< 65 Y



≥ 65 Y



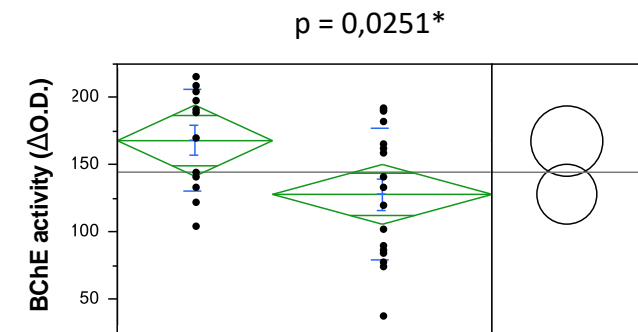
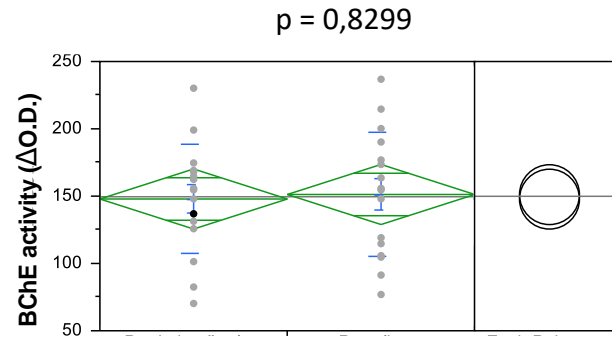
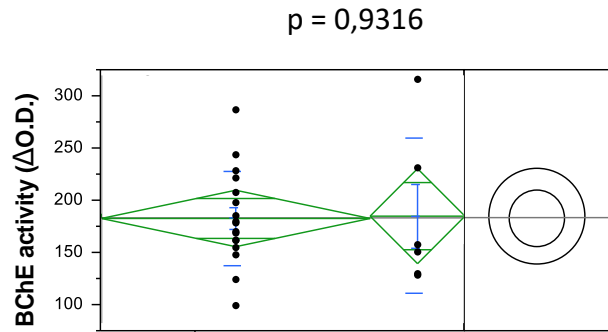
Môže byť BChE prognostickým markerom COVID-19?

PREPUSTENÍ

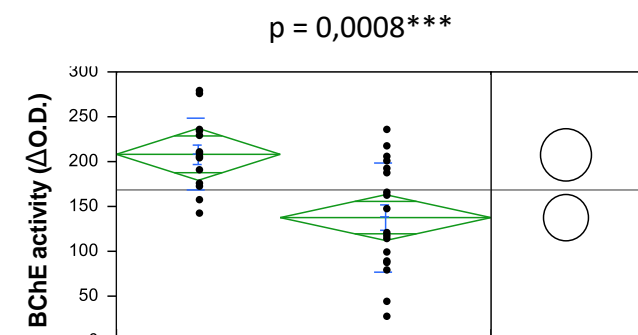
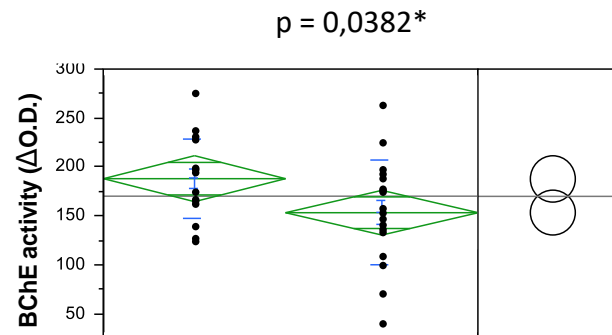
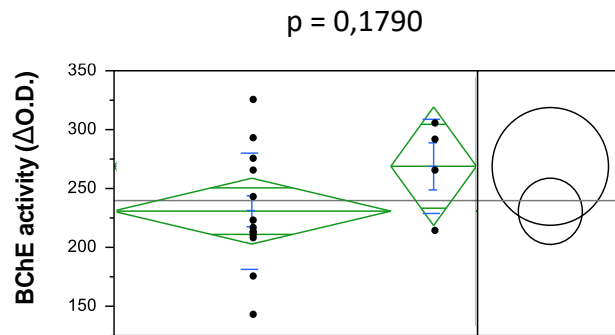
PRELOŽENÍ

NEPREŽIVŠÍ

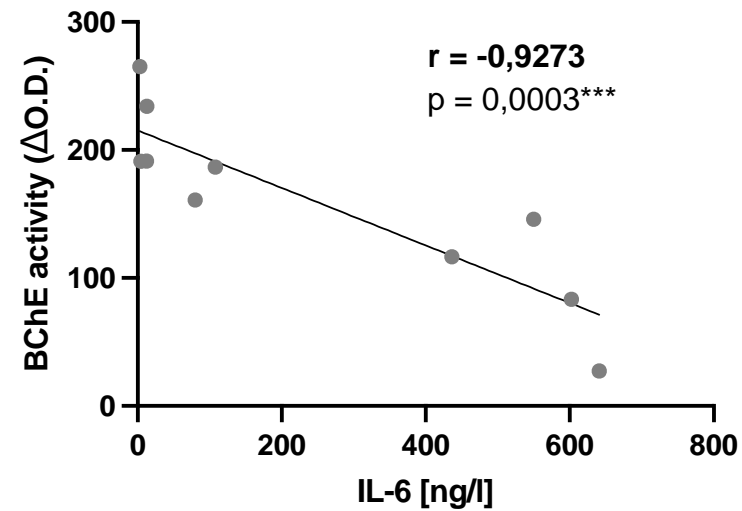
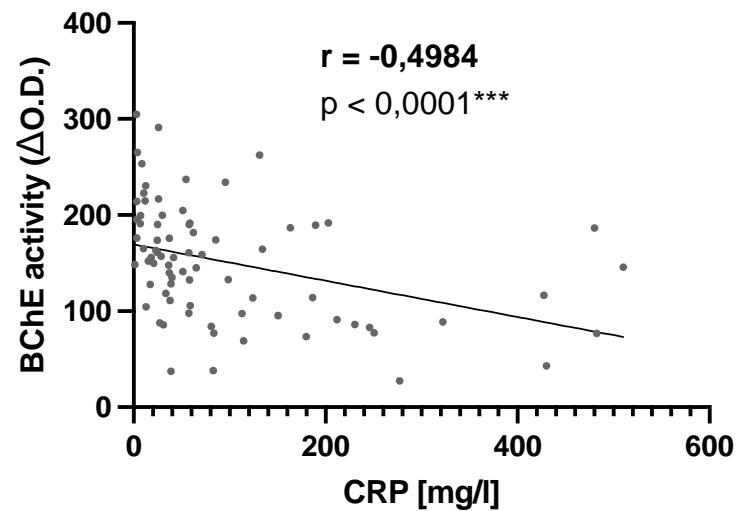
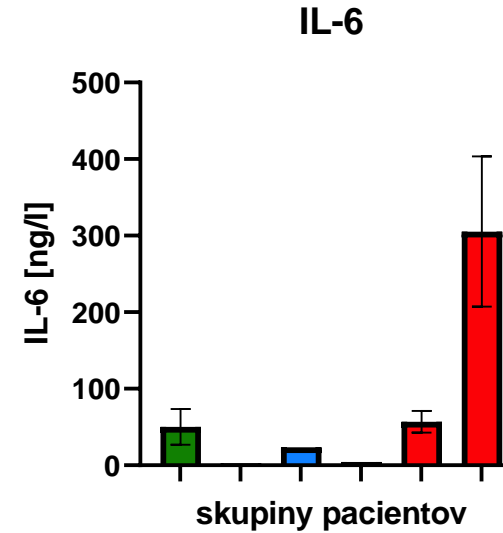
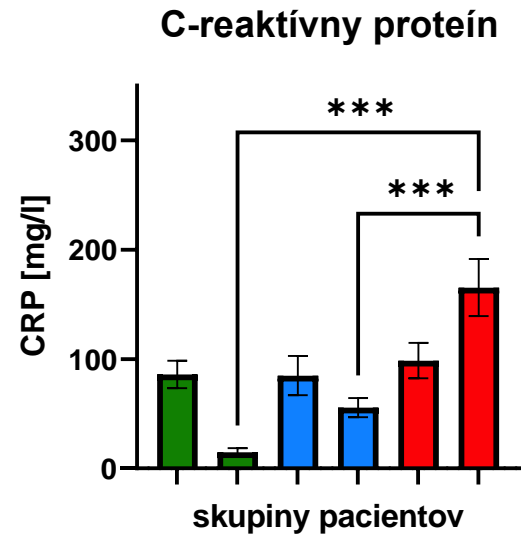
BMI < 30



BMI \geq 30



Môže byť BChE prognostickým markerom COVID-19?



Môže byť BChE prognostickým markerom COVID-19?

Sérová aktivita BChE sa progresívne znižovala v skupine nepreživších pacientov hospitalizovaných s ťažkým priebehom COVID-19

- nezávisle od pohlavia
- nezávisle od veku
- nezávisle od BMI
- nezávisle od komorbidít (kvantitatívne ani kvalitatívne)
- korelujúc so zápalovými markermi

Čo ďalej?

- Pokračovanie v analýze zdravotnej dokumentácie
- Model predikcie úmrtia u pacientov s COVID-19
- Analýza > 500 pacientov s alfa a delta variantom COVID-19
- Analýza sér pacientov s Wuhan typom COVID-19 s rôzne závažným priebehom

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SEKCIA
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LEKÁRNIKOV

Farmaceutická starostlivosť pre špecifické skupiny pacientov

13. - 14.10.2022, Falkensteiner Hotel Bratislava****

Slovenskej lekárskej komory

Finančná podpora: VEGA (1/0815/21; 1/0855/15),
APVV (SK-FR-19-0005; SK-FR-0048-11; SK-FR-0031-09)



EUROPEAN UNION
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MINISTRY
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Dingová D., Paul Hrabovská A.

T. Fazekáš



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hrabovska@fpharm.uniba.sk
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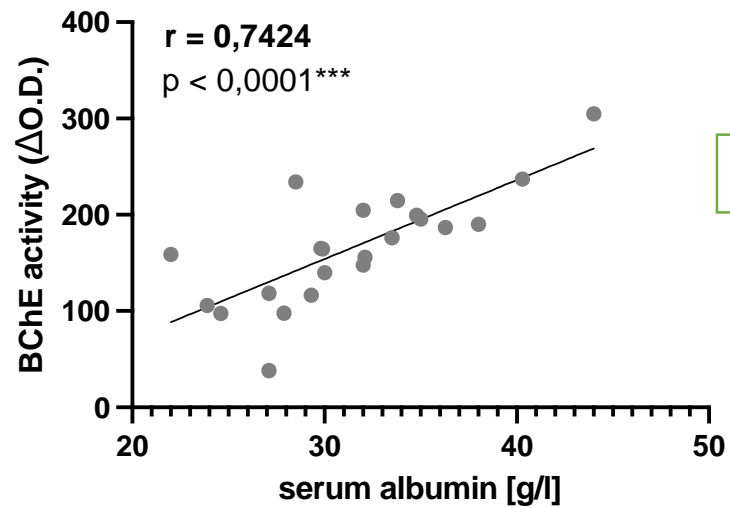
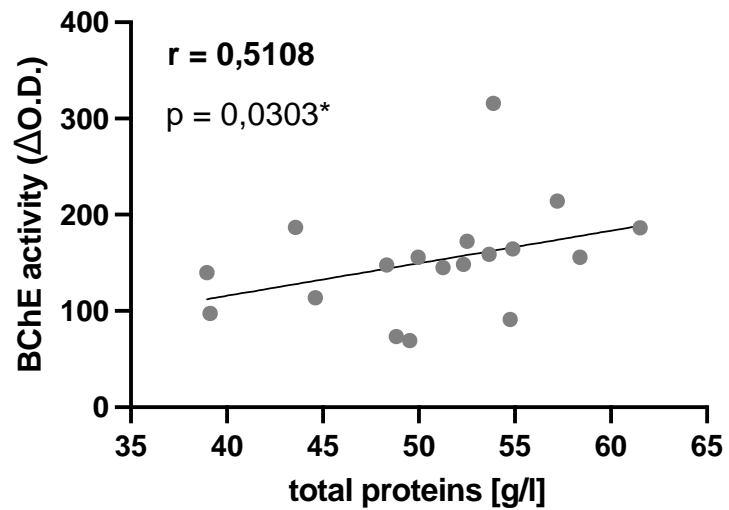
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v Bratislave



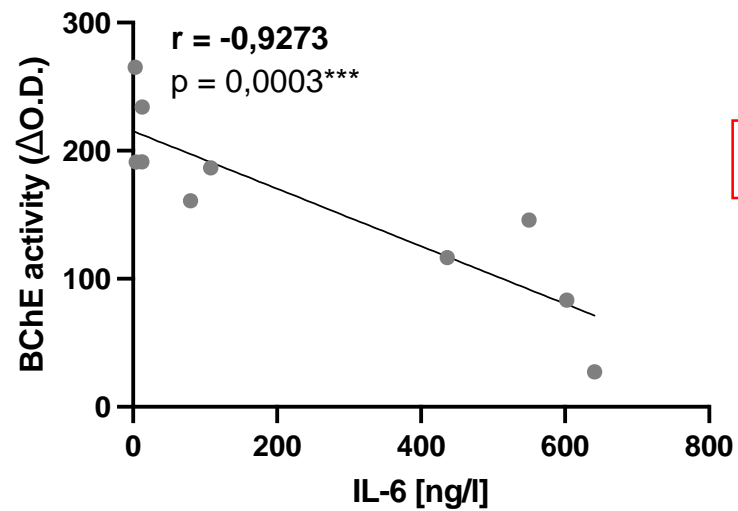
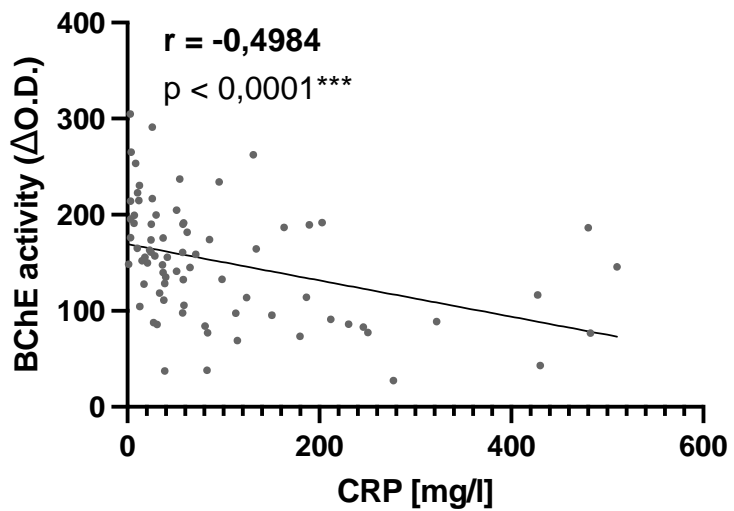
SLOVENSKÁ
ZDRAVOTNICKÁ
UNIVERZITA



FAKULTNÁ NEMOCNICA
TRNAVA



Pozitívna korelácia

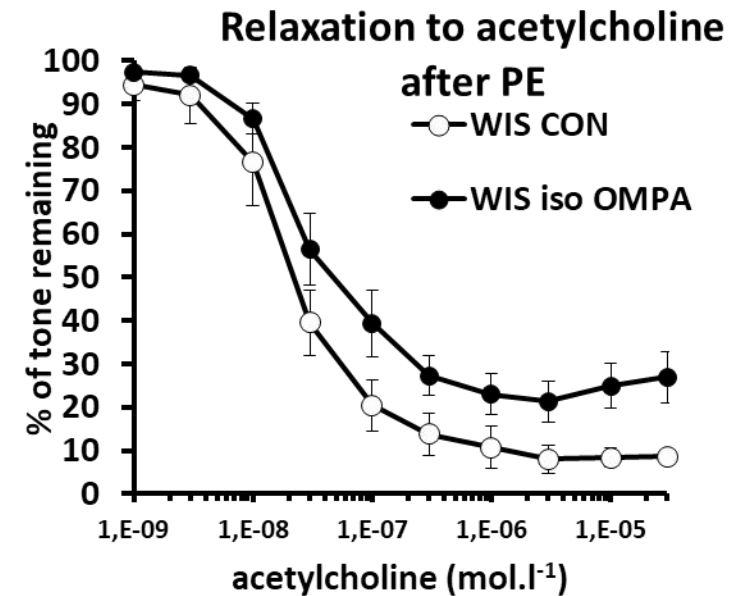
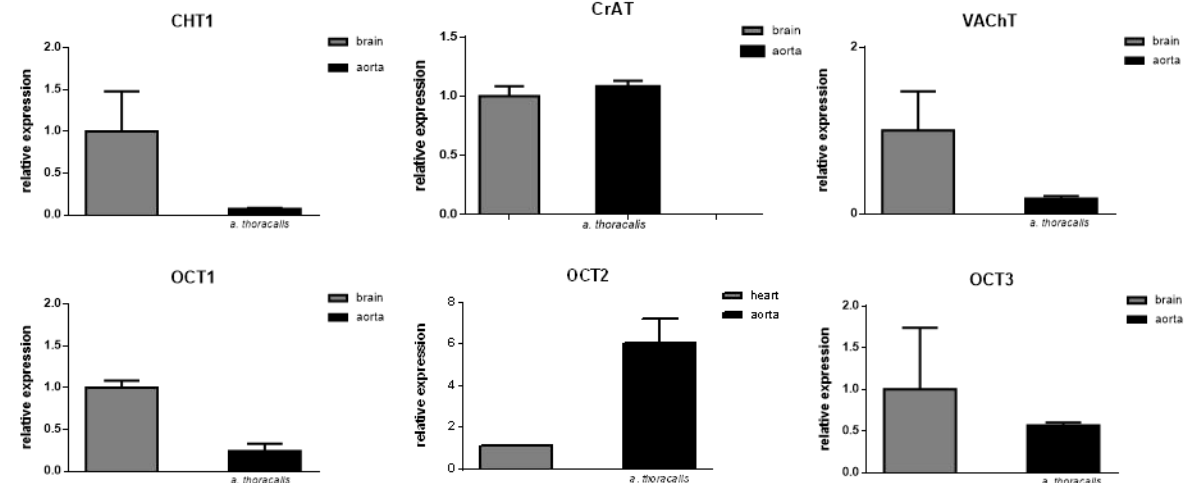
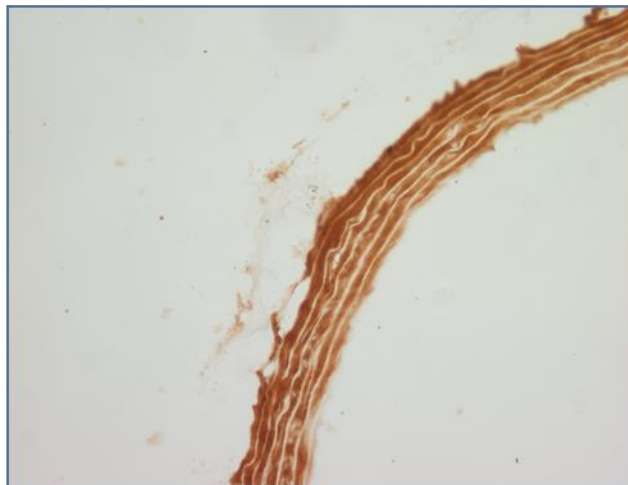
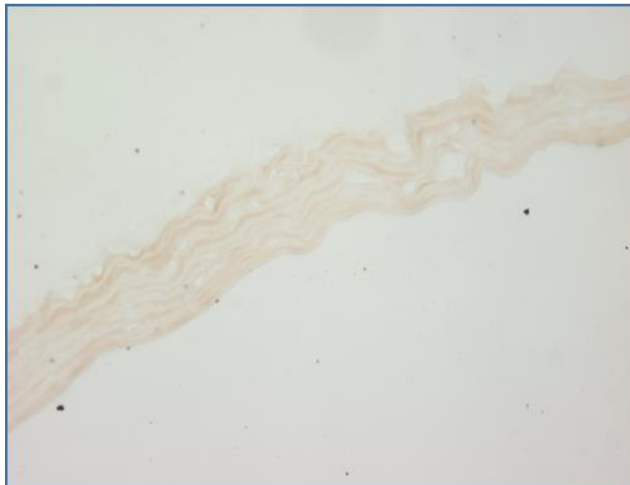
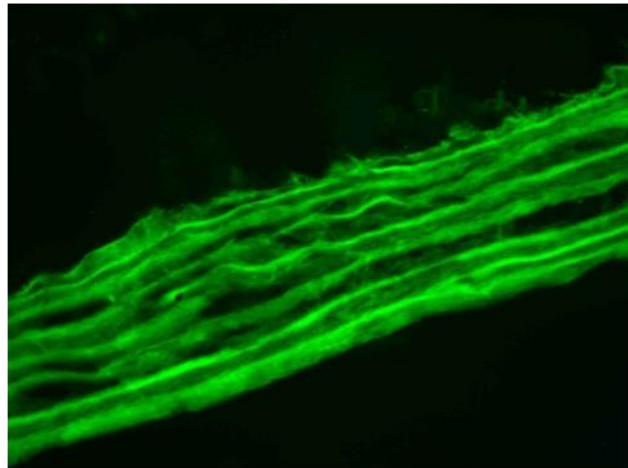
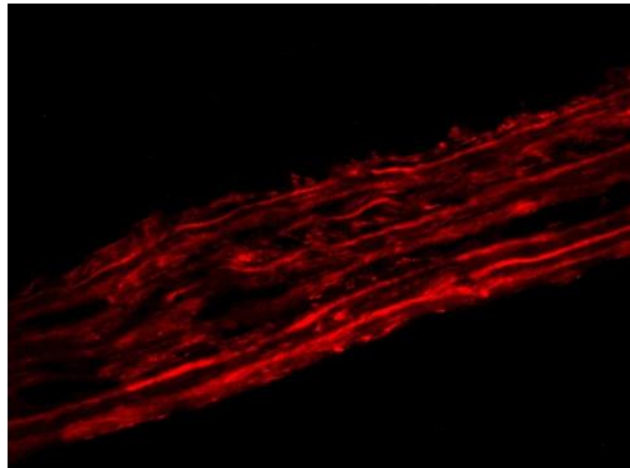


Negatívna korelácia

Cholínergický systém v cievach

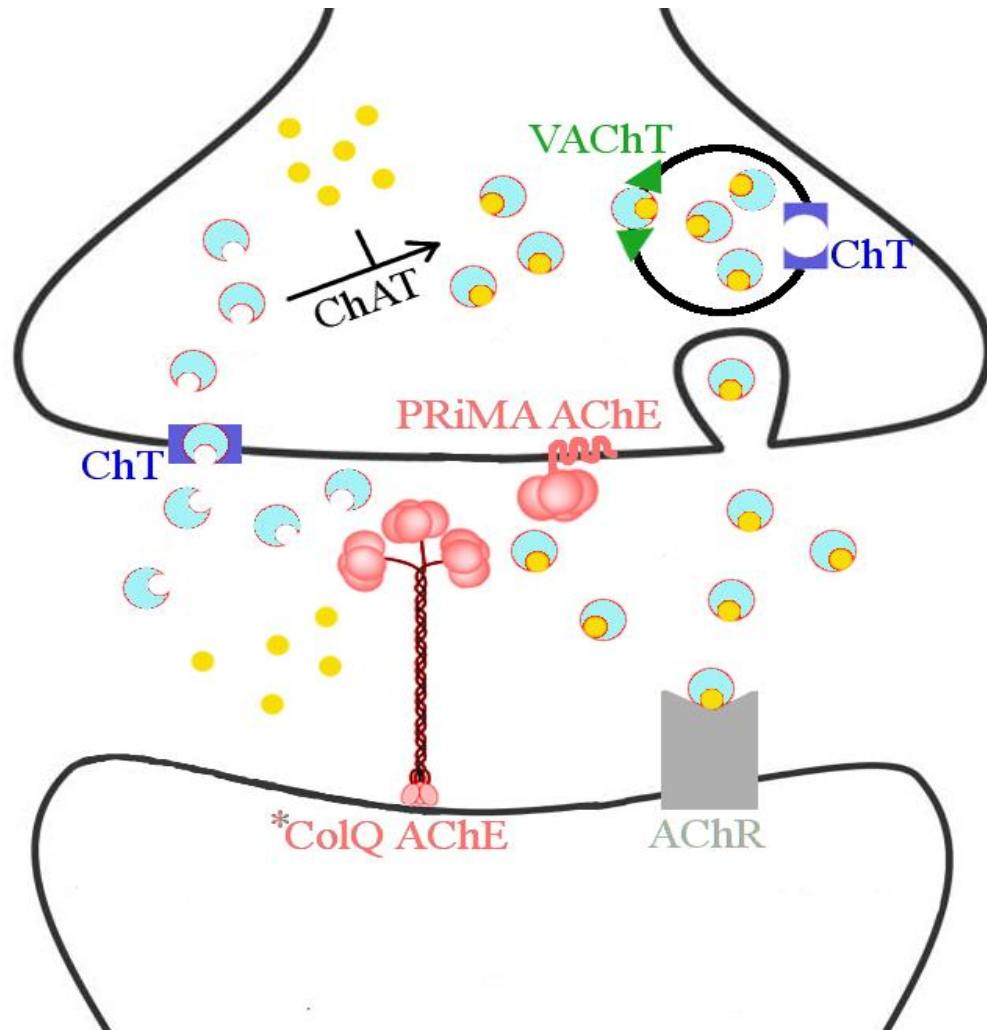
AChE

BChE

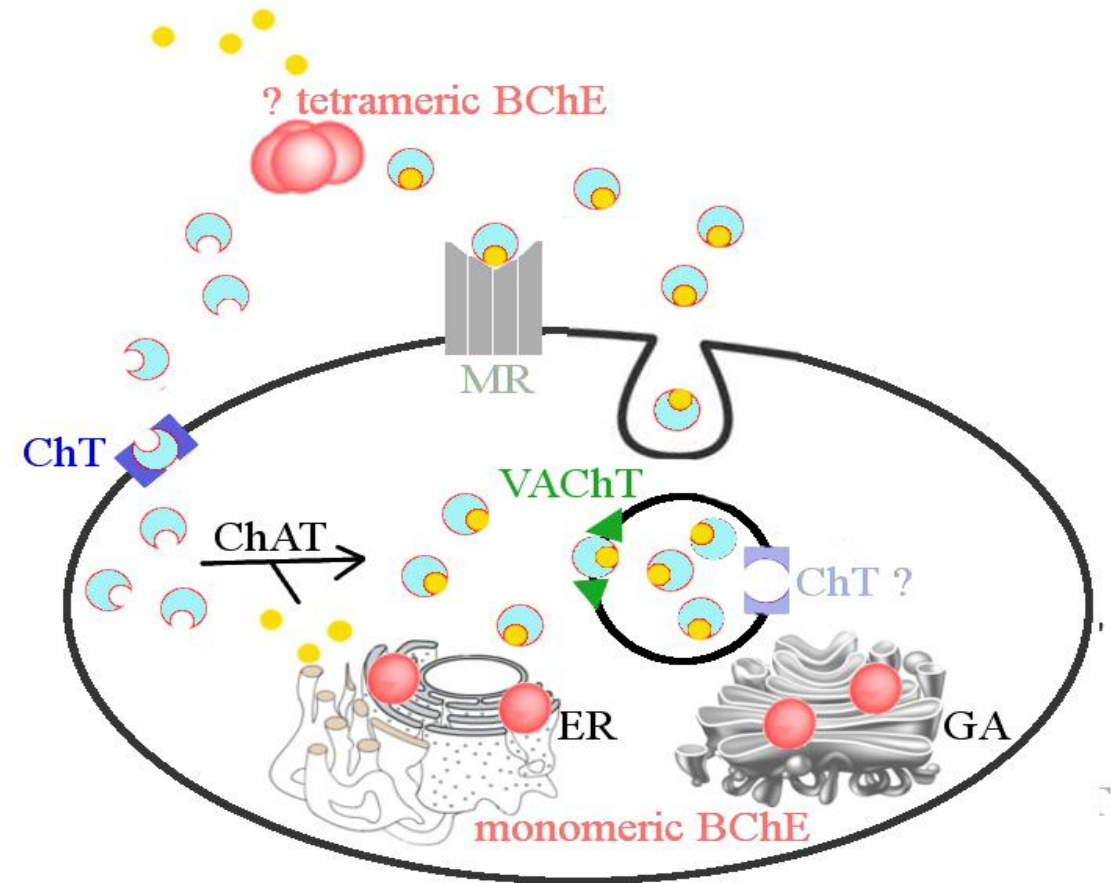


Cholínergický systém srdca

Neuronálny



Neneuronálny



BChE vs. rizikové faktory ťažkého COVID-19

 Molecular Medicine

Cholinergic Activity as a New Target in Diseases of the Heart

Ashbeel Roy,^{1,2} Silvia Guatimosim,³ Vania F Prado,^{1,2,4} Robert Gros,^{1,2,5} and Marco A M Prado^{1,2,4}

¹Robarts Research Institute, The University of Western Ontario, London, Ontario, Canada; ²Department of Physiology and Pharmacology, The University of Western Ontario, London, Ontario, Canada; ³Department of Physiology and Biophysics, Institute of Biological Sciences, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; ⁴Department of Anatomy and Cell Biology, The University of Western Ontario, London, Ontario, Canada; and ⁵Department of Medicine, University of Western Ontario, London, Ontario, Canada

The autonomic nervous system is an important modulator of cardiac signaling in both health and disease. In fact, the significance of altered parasympathetic tone in cardiac disease has recently come to the forefront. Both neuronal and nonneuronal cholinergic signaling likely play a physiological role, since modulating acetylcholine (ACh) signaling from neurons or cardiomyocytes appears to have significant consequences in both health and disease. Notably, many of these effects are solely due to changes in cholinergic signaling, without altered sympathetic drive, which is known to have significant adverse effects in disease states. As such, it is likely that enhanced ACh-mediated signaling not only has direct positive effects on cardiomyocytes, but it also offsets the negative effects of hyperadrenergic tone. In this review, we discuss recent studies that implicate ACh as a major regulator of cardiac remodeling and provide support for the notion that enhancing cholinergic signaling in human patients with cardiac disease can reduce morbidity and mortality. These recent results support the idea of developing large clinical trials of strategies to increase cholinergic tone, either by stimulating the vagus or by increased availability of ACh, in heart failure.

Online address: <http://www.molmed.org>

doi: 10.2119/molmed.2014.00125

**KVS
OCHORENIA**

Srdcové zlyhanie
Hypertenzia
Ventrikulárne arytmie
Protektívne pri IM
↓ KV mortality

Calderon-Margalit et al. (2006) Clin Chem
Roy A (2015) Molecular Medicine
Roy et al. (2013) FASEB
Lataro et al. (2013) AJP
Androne et al. (2003) Heart
Bharadwaj et al. (2017) Clin Exp Pharm Phys
Serra et al. (2009) J Card. Fail
Kakinuma et al. (2013) JAHA

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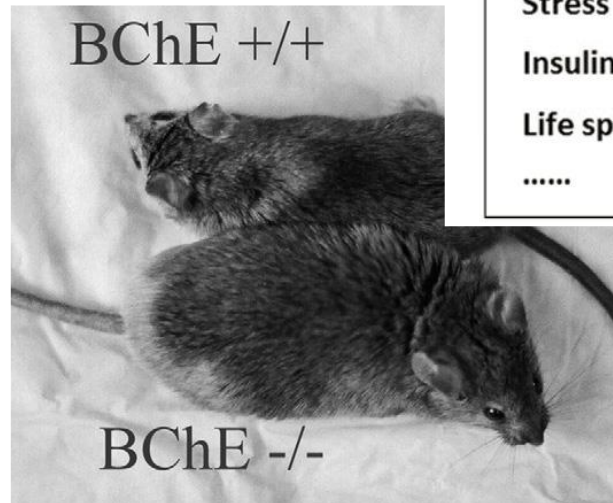


Ľudskí jedinci s homozygotnou formou silentnej formy BChE; komunita Vysya v Indii

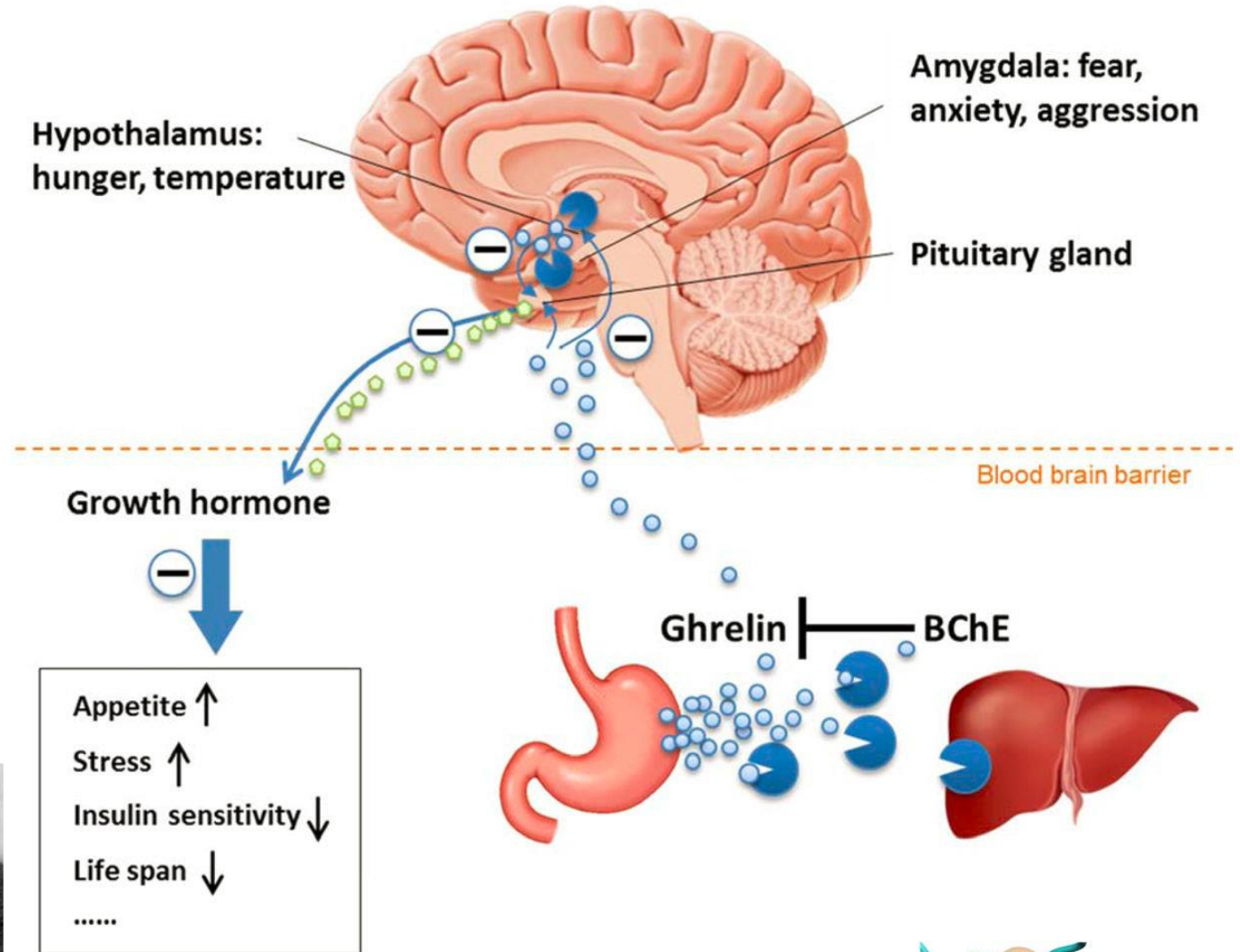
Duysen E.G. et al. (2009) Expert Opin. Drug Metab. Toxicol.
 Manoharan et al. (2006) Clinica Chimica Acta



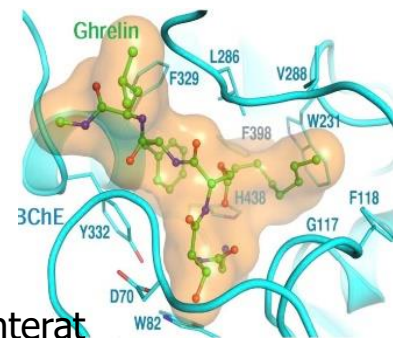
Li B. et al. (2006) J Mol Neurosci 2006



Li B. et al. (2008) Chem. Biol. Interact.

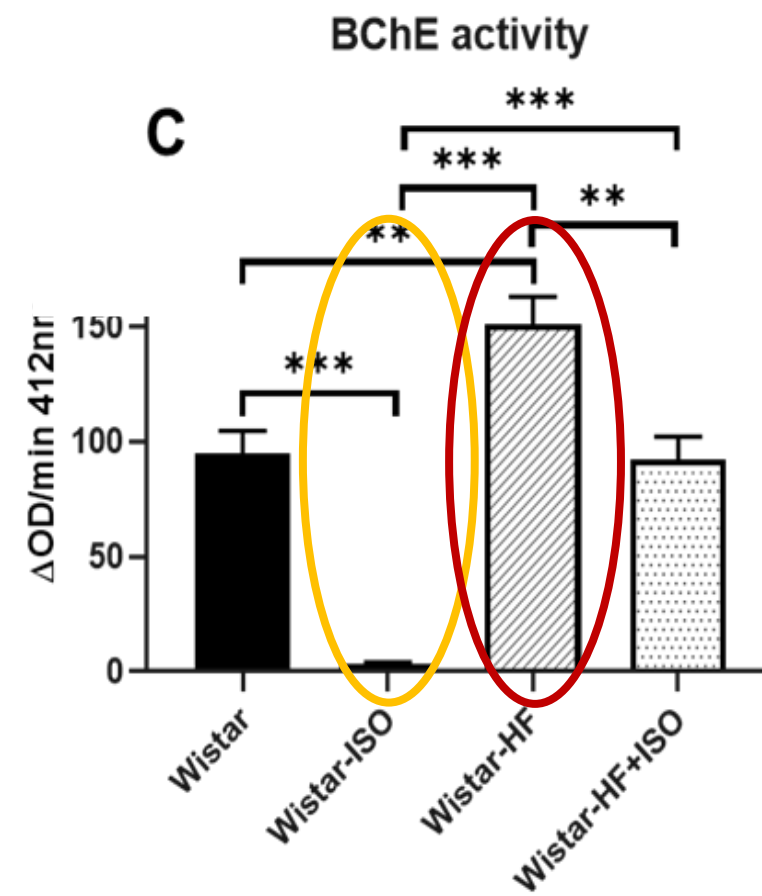
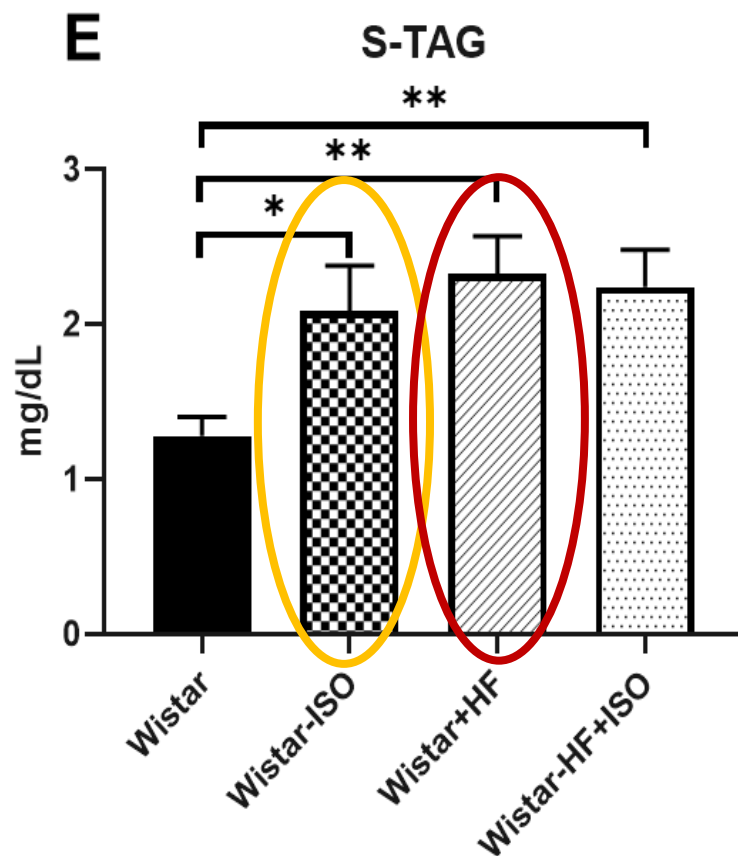
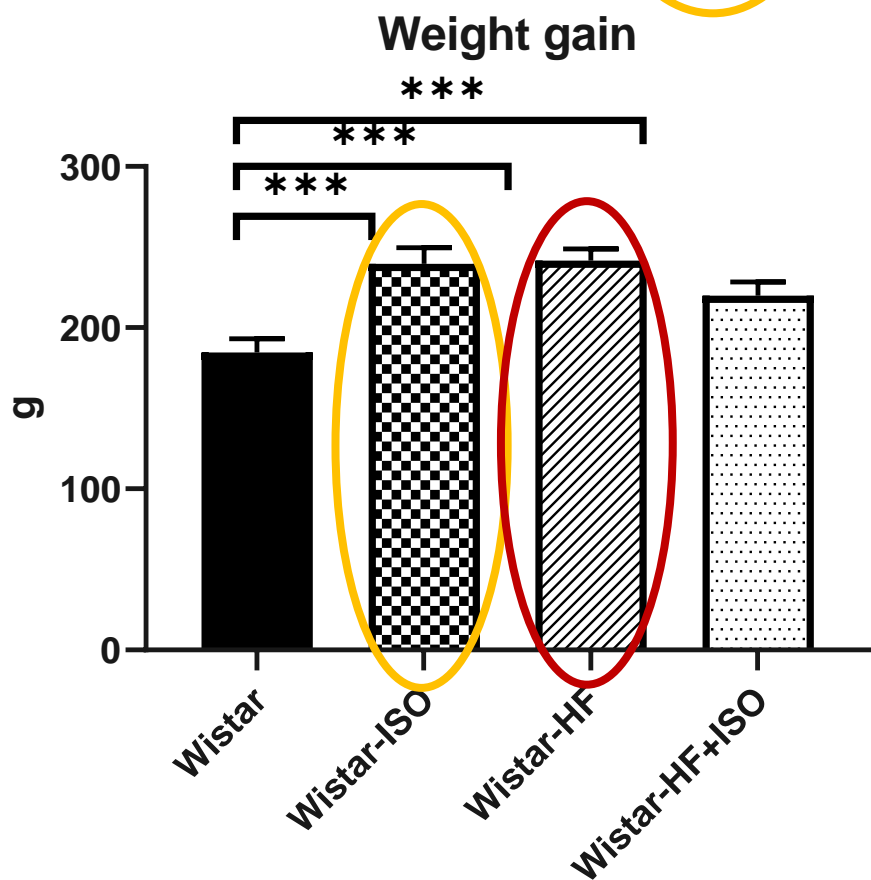


Chen V et al. (2017) PNAS
 Brimijoin S et al. (2016) Chem Biol Interact

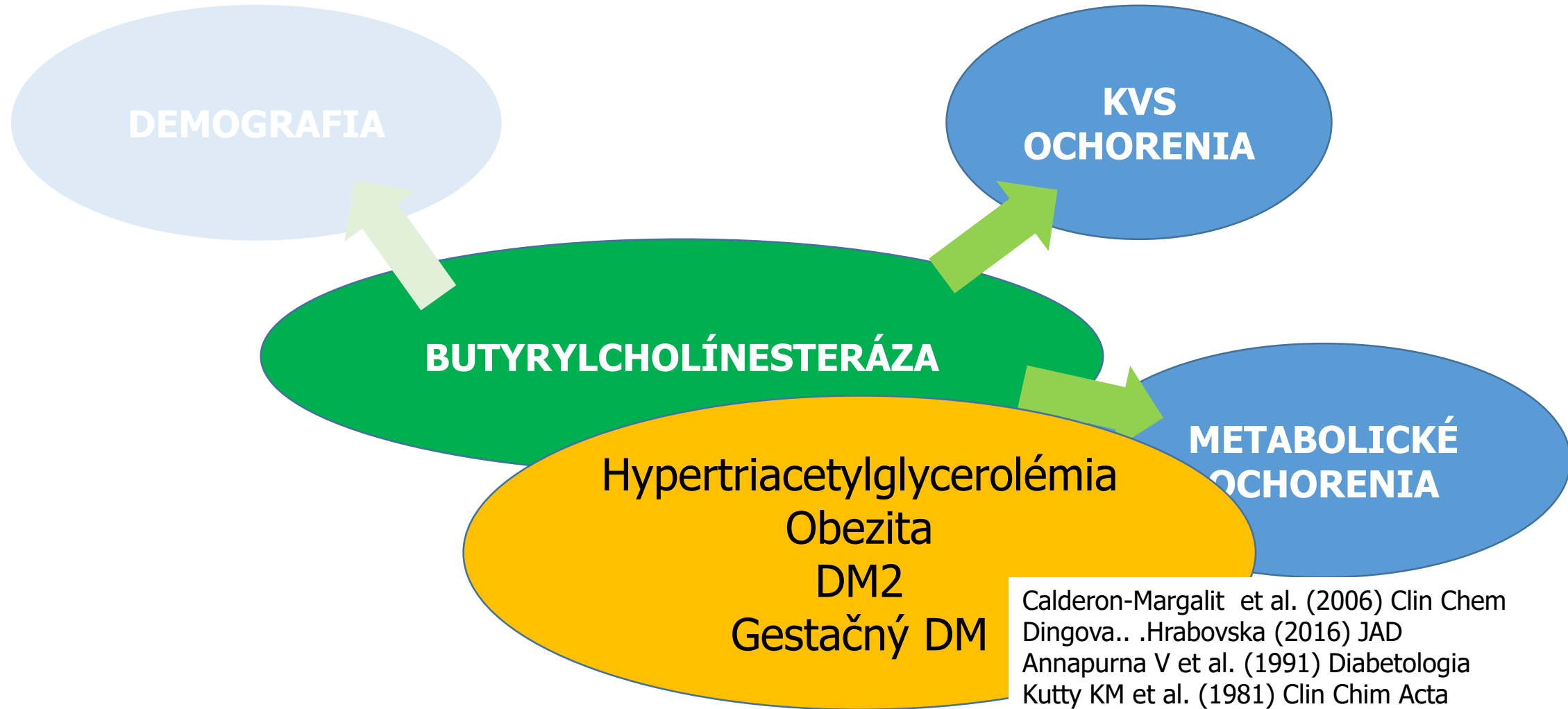


Príjem potravy	kontrola	iso-OMPA	HF	iso-OMPA +HF
g/deň	44.94 ± 0.49	47.46 ± 1.50	43.79 ± 0.59	42.06 ± 0.45
kcal/deň	145.0 ± 1.59	153.1 ± 4.82	196.9 ± 2.66*	189.2 ± 2.05*

HF – vysokotuková strava (20% bravčová masť)
 Iso-OMPA = selektívny inhibítor BChE



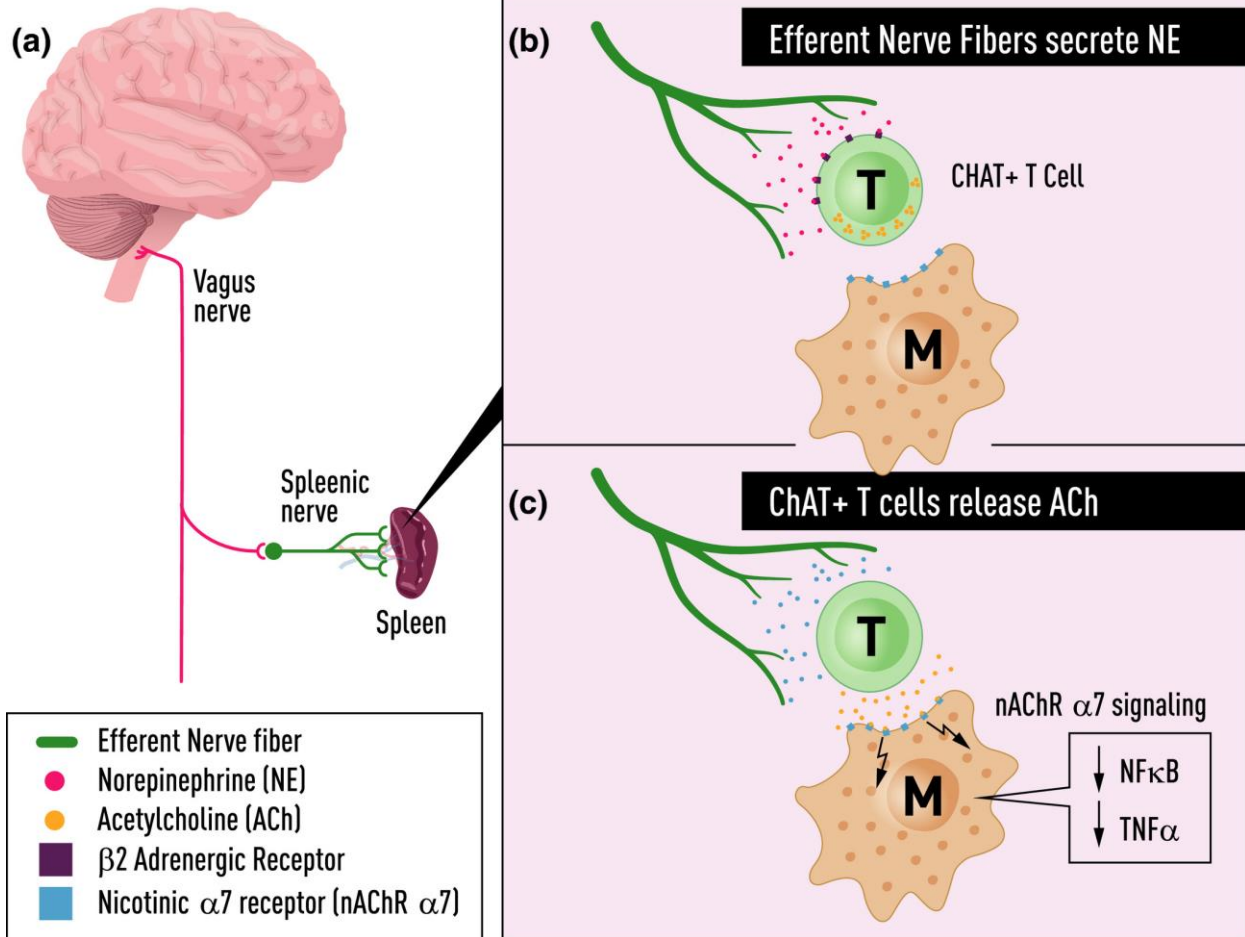
BChE vs. rizikové faktory těžkého COVID-19



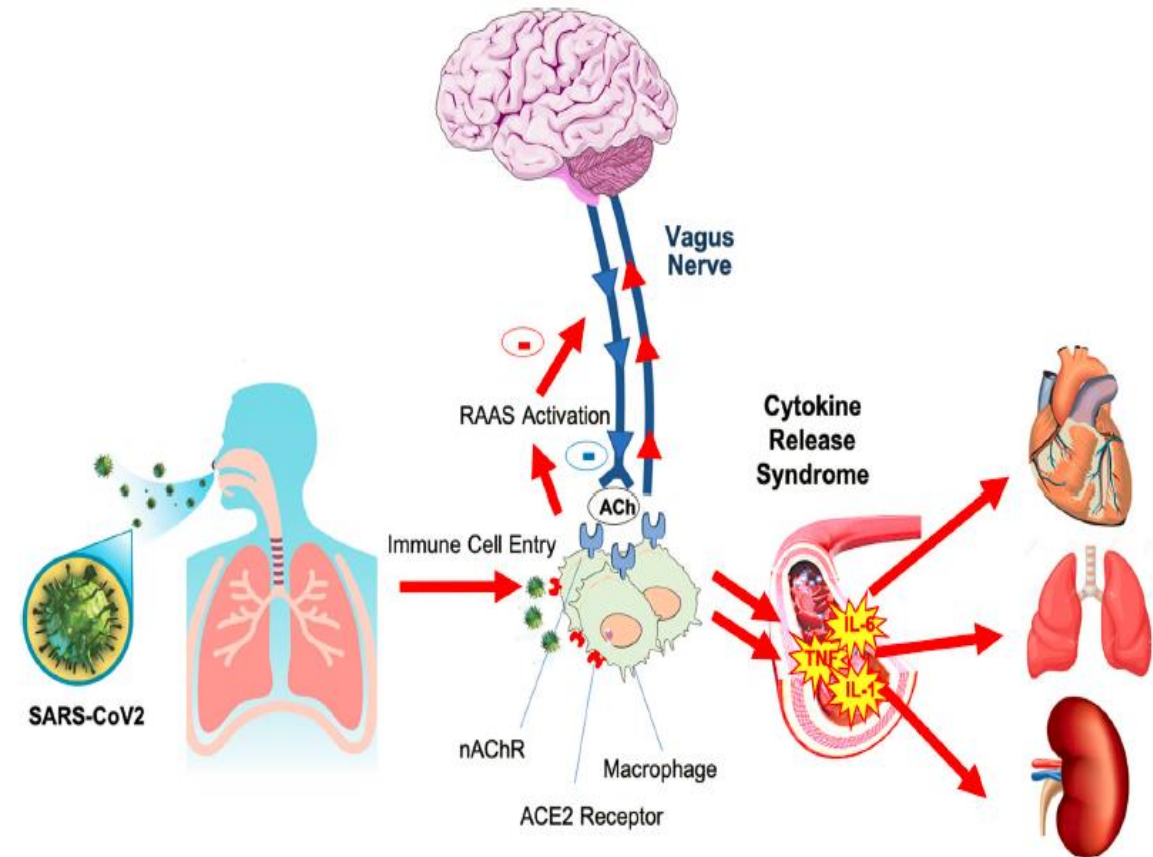
Calderon-Margalit et al. (2006) Clin Chem
Dingova.. Hrabovska (2016) JAD
Annapurna V et al. (1991) Diabetologia
Kutty KM et al. (1981) Clin Chim Acta
Vallianou N. et al. (2014) J Cardiovasc. Med.
Larissa O. Guimarães (2014) Genet Mol Biol.
...

Imunomodulačný účinok acetylcholínu

Vagus nerve stimulation in sepsis



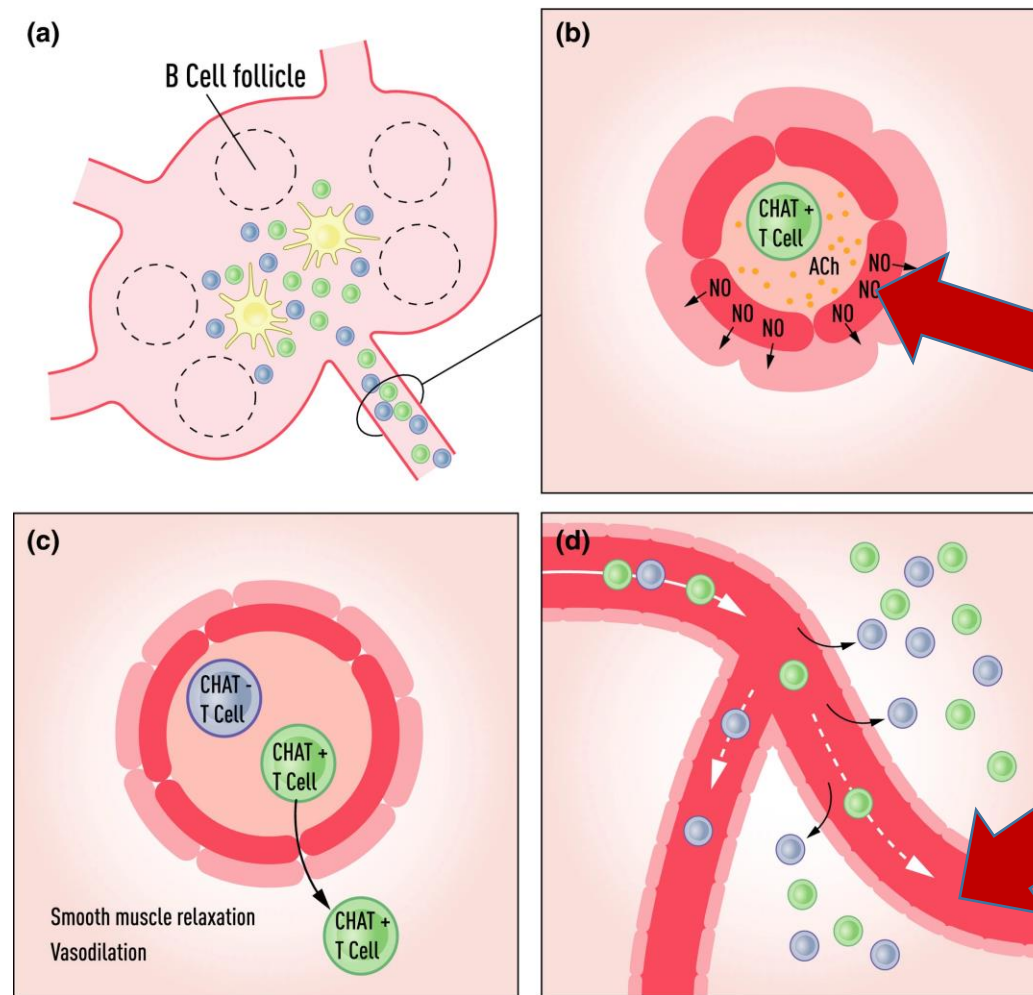
Pomara N. (2020) Med Hypotheses



Fudim M et al. (2019) J Cardiovasc Transl Res.

Imunomodulačný účinok acetylcholínu

ChAT-expressing T cells during infection

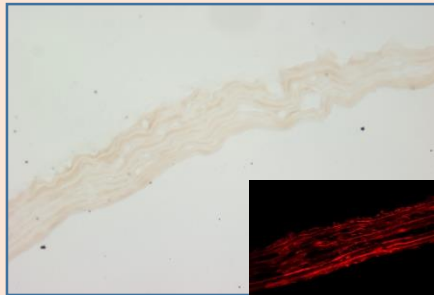


BChE

Butyrylcholinesteráza v cievach

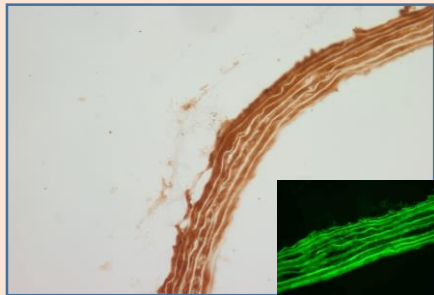
Potkan

Cieva



AChE

Plazma

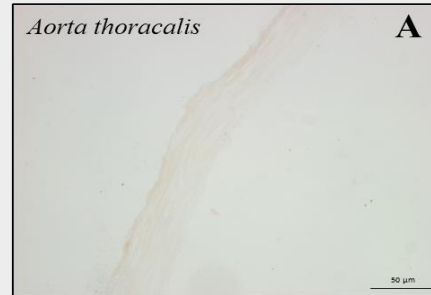


BChE

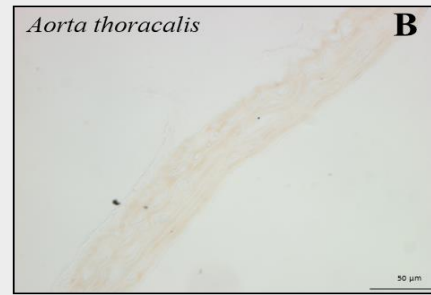


Myš

Cieva



Plazma



Človek

Cieva

?

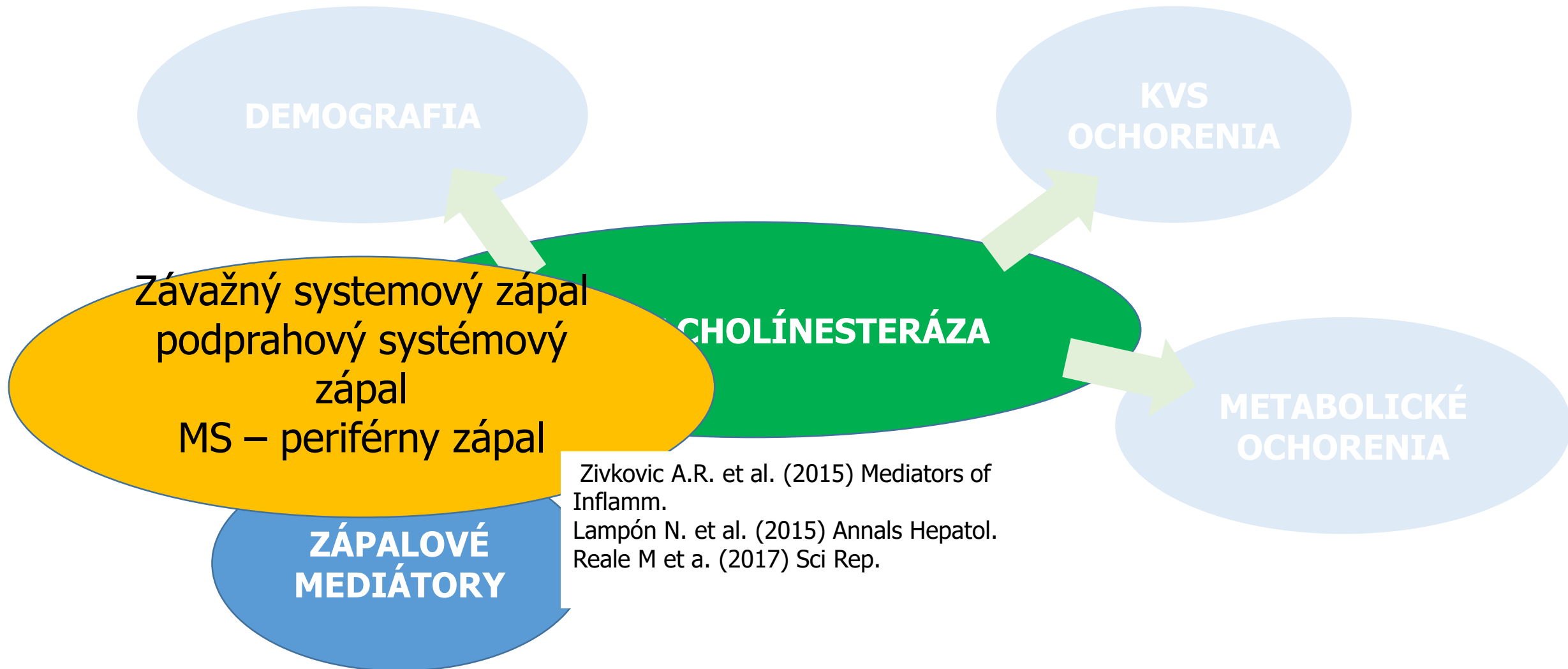
Plazma



?



BChE vs. rizikové faktory t'azkého COVID-19



DEMOGRAFIA

KVS
OCHORENIA

Závažný systémový zápal
podprahový systémový
zápal
MS – periférny zápal

CHOLÍNESTERÁZA

METABOLICKÉ
OCHORENIA

ZÁPALOVÉ
MEDIÁTORY

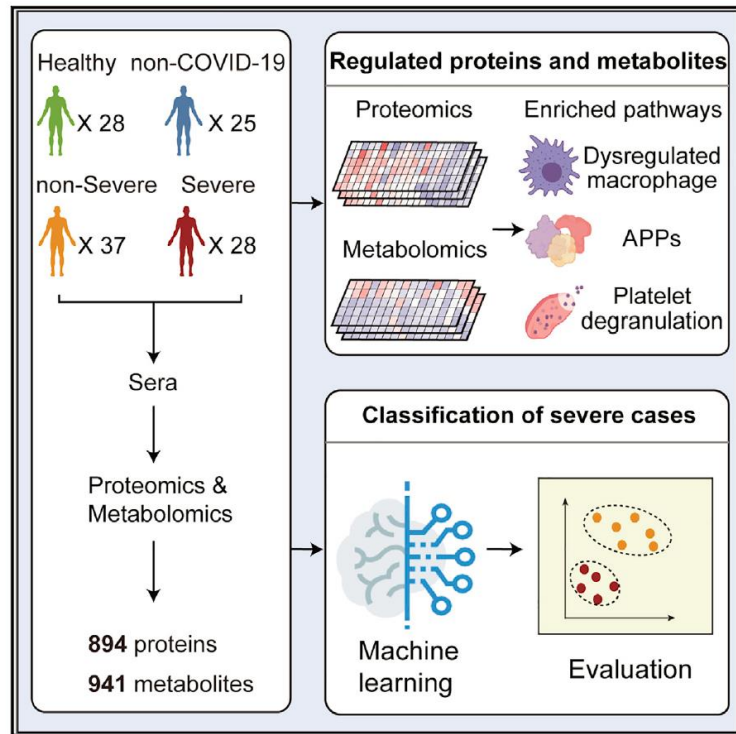
Zivkovic A.R. et al. (2015) Mediators of Inflamm.

Lampón N. et al. (2015) Annals Hepatol.

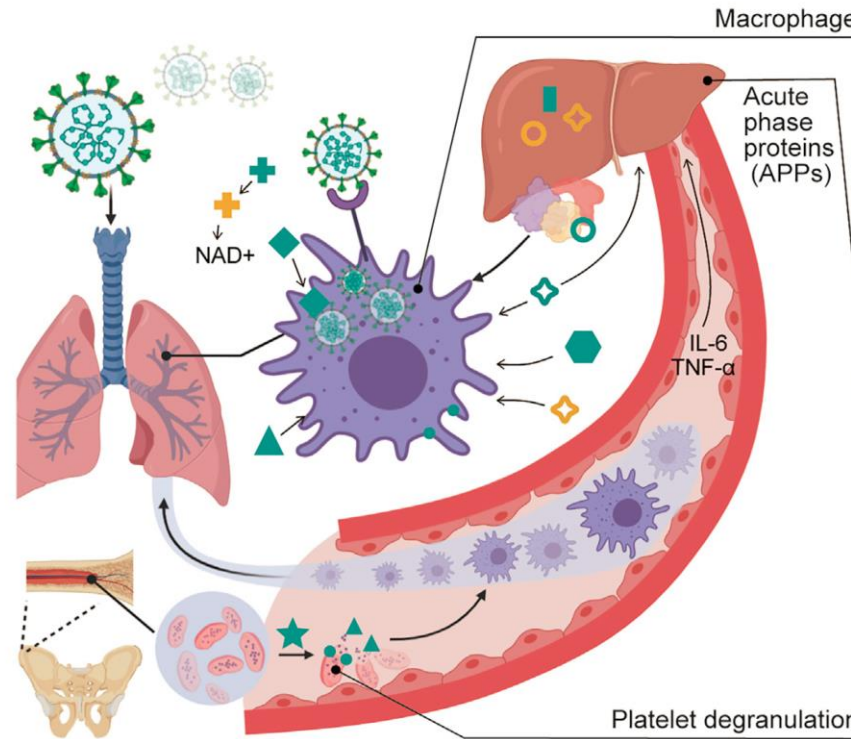
Reale M et a. (2017) Sci Rep.

Rizikové faktory ťažkého priebehu COVID-19

Metabolomika a proteomika



Metabolická a imunitná dysregulácia



93 proteínov

APOA1	APOA2
1 2 3 4	1 2 3 4
APOH	APOD
1 2 3 4	1 2 3 4
APOM	APOL1
1 2 3 4	1 2 3 4
SAA1	SAA2
1 2 3 4	1 2 3 4
CRP	SERPINA3
1 2 3 4	1 2 3 4
ORM1	C6
1 2 3 4	1 2 3 4
CFB	CPN1
1 2 3 4	1 2 3 4
PPBP	PF4
1 2 3 4	1 2 3 4

204 metabolitov

- Bilirubin products
- Choline
- Fatty acids
- Glycerophospholipids
- Serotonin
- Sphingolipids
- Tryptophan
- Kynurenine derivatives
- Mannose
- Glucuronate
- Steroid hormones
- Bile acid derivatives

1 Healthy
 2 non-COVID-19
 3 non-Severe
 4 Severe

Z-Score protein / metabolite abundance
 1 0 -1

Čo sú rizikové faktory závažného priebehu COVID-19?

- European Centre for Disease Prevention and Control
 - <https://www.ecdc.europa.eu>
- National Institutes of Health (NIH)
 - www.nih.gov
- WHO | World Health Organization
 - <https://www.who.int>
- Centers for Disease Control and Prevention
 - <https://www.cdc.gov>

- PubMed.gov
<https://pubmed.ncbi.nlm.nih.gov/>

The screenshot shows a PubMed search interface. The search bar contains the text "covid-19 risk factors severe". Below the search bar, there are buttons for "Save", "Email", and "Send to". The search results are sorted by "Most recent" and there are 8,155 results. A "RESULTS BY YEAR" bar chart shows a significant increase in results in 2022 compared to 2019. A notification box suggests using COVID-19 filters from PubMed Clinical Queries to refine the search. At the bottom, there is a suggestion: "Did you mean covid-19 risk factors severe (18,718 results)?"

PubMed.gov

covid-19 risk factors severe

Advanced Create alert Create RSS User Guide

Save Email Send to

Sorted by: Most recent

Display options

MY NCBI FILTERS

8,155 results

Page 1 of 816

RESULTS BY YEAR

2019 2022

Use COVID-19 filters from PubMed Clinical Queries to refine your search

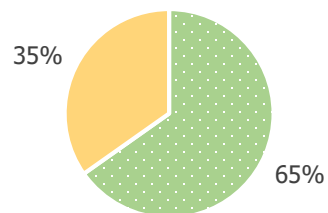
Treatment Mechanism Transmission More filters

See more SARS-CoV-2 literature, sequence, and clinical content from NCBI

Did you mean covid-19 risk factors severe (18,718 results)?

n = 148

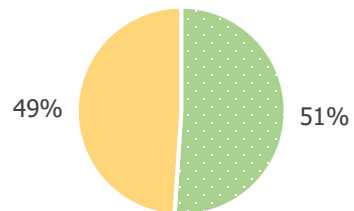
**Prepustení
n = 46 (31 %)**



■ normal ■ obese

30,05 (19,9 – 50,1)*

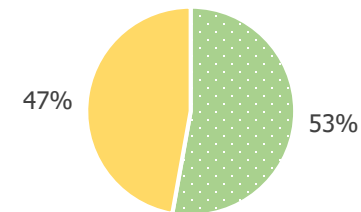
**Preložení
n = 49 (33 %)**



■ normal ■ obese

30,75 (17,6 – 50,2)*

**Nepřeživší
n = 53 (36 %)**



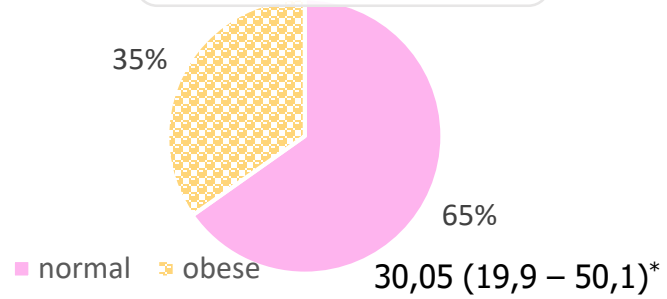
■ normal ■ obese

31,45 (16,7 – 44,2)*

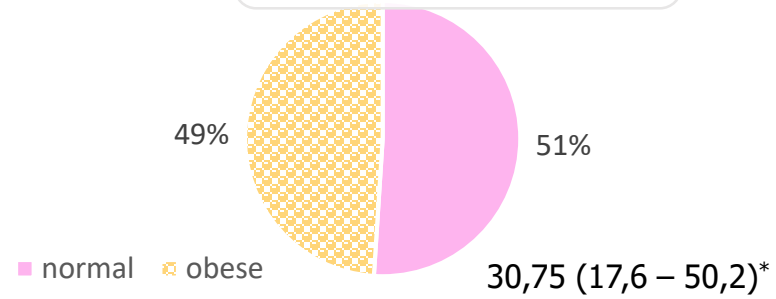
*average (min – max)

n = 148

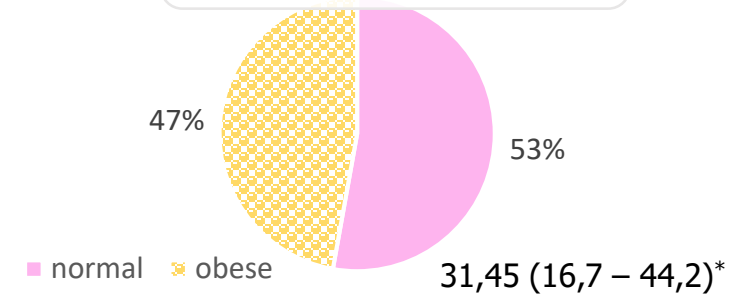
**Prepustení
n = 46 (31 %)**



**Preložení
n = 49 (33 %)**



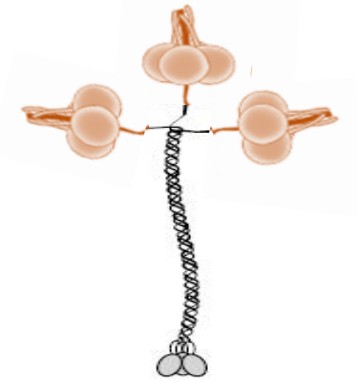
**Nepřeživší
n = 53 (36 %)**



*average (min – max)



Butyrylcholinesteráza (BChE)



Orgán	BChE (U/g)	AChE (U/g)
Pečeň	10,64 ± 1,48	9,41 ± 0,06
Plúca	8,62 ± 0,26	0,86 ± 0,07
Slezina	7,06 ± 0,11	1,5 ± 0,20
Žalúdok	7,05 ± 0,44	0,98 ± 0,08
Obličky	6,56 ± 0,35	0,68 ± 0,14
Tenké črevo	6,20 ± 0,21	0,90 ± 0,04
Mozoček	6,05 ± 0,29	9,30 ± 1,22
Plazma	5,6 ± 1,2	0,008 ± 0,001
Predĺžená miecha	3,6 ± 0,27	20,03 ± 0,76
Mozgová kôra	2,93 ± 0,28	2,13 ± 0,37
Srdce	2,56 ± 0,16	1,03 ± 0,16
Kostrový sval	1,97 ± 0,14	3,75 ± 0,32
Koža	1,83 ± 0,23	0,99 ± 0,6
Štítna žľaza	0,57 ± 0,13	0,67 ± 0,02

Funkcia

1. ?
2. hydrolýza ACh
3. hydrolýza xenobiotík
(sukcinylcholín, kokaín, ASA,)
4. scavenging OP
5. vzťah s viacerými patológiami
(napr. obezita, MS, DM)

**BChE JE VO VZŤAHU
S RIZIKOVÝMI FAKTORMI
ZÁVAŽNÉHO PRIEBEHU
COVID-19!**