

Results of the SEARCH registry

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SEARCH-COVID-19

 SepsEAst Registry to define the CHaracteristics in COronaVIrus Disease 2019

Aim of the study

 to collect structured data from ICUs within the SepsEast community during the COVID-19 pandemic Methods

Study design and setting

- originally the study was designed to be a prospective registry
- due to overwhelming workload and staff shortages during the actual COVID-19 waves it was impossible to prospectively enrol patients and collect data
- data were collected retrospectively within the time period of 01.03.2020 - 28.02.2021, encompassing the first surge in Spring and second wave in Autumn 2020
- participating centres were all related to the major SepsEast collaborators within Central and Eastern Europe
- 11 centers in 6 countries



	Country – Centre
	CROATIA
	University Hospital Rijeka
	CZECHIA
	University Hospital Plzen
	HUNGARY
	Flór Ferenc Hospital County Pest
	University of Pécs, School of Medicine
	POLAND
7	Poznań Medical University Hospital
	Central Clinical Hospital of the Ministry of Interior and Administration, Warsaw
	SLOVAKIA
٦	University Hospital Nitra
	University Hospital Nové Zámky
	University Hospital Banska Bystrica
٦	SLOVENIA

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General Hospital Celje

General Hospital Murska Sobota

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Patients

- All consecutive adult patients admitted to the ICU due to COVID-19 pneumonia within the dedicated time period were found eligible
- Patients admitted with severe acute respiratory failure due to other reasons than coronavirus 2 (SARS-CoV-2), but in whom SARS-CoV-2 screening proved positive on hospital or ICU admission, were excluded

Main outcome

- all-cause in-hospital mortality (understood as case fatality)
 - defined as a death during ICU stay or death occurring after transfer from ICU to the ward during the same hospitalization
- there was no censoring nor missing data of the main (primary) outcome
- the most probable cause of death was identified by using the methodology of a study by Contou et al. (Causes and timing of death in critically ill COVID-19 patients. Crit Care. 2021;25:79)
- orders to either withhold or withdraw treatment were also screened

Other collected data

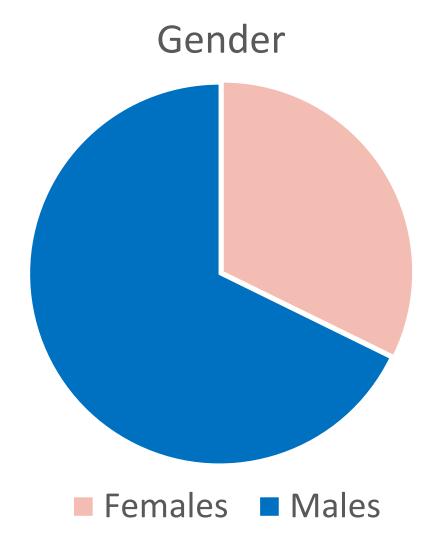
- baseline demographic parameters and comorbidities
- time describing parameters (i.e. symptom onset, date of first proved SARS-CoV-2 positivity, admission and discharge/death dates)
- parameters of **organ support** (i.e. mode and length of ventilator support, other vital organ supports such as vasoconstrictors, inotropes, RRT)
- treatment (corticosteroids, anti-viral and disease modifying drugs, anticoagulation)
- ICU stay related **complications** (i.e. deep-vein thrombosis, pulmonary embolism, barotrauma)
- laboratory parameters on ICU admission (i.e. leukocyte, lymphocyte count, C-reactive protein, procalcitonin level, PaO₂/FiO₂ ratio)

Results

	No of ICU	Percentage of
Country – Centre	patients	the dataset
CROATIA	286	13%
University Hospital Rijeka	286	13%
CZECHIA	<i>583</i>	27%
University Hospital Plzen	583	27%
HUNGARY	269	13%
Flór Ferenc Hospital County Pest	112	5%
University of Pécs, School of Medicine	157	7%
POLAND	115	5%
Poznań Medical University Hospital	66	3%
Central Clinical Hospital of the Ministry of Interior and		
Administration, Warsaw	49	2%
SLOVAKIA	491	23%
University Hospital Nitra	178	8%
University Hospital Nové Zámky	166	8%
University Hospital Banska Bystrica	147	7%
SLOVENIA	395	18%
General Hospital Celje	226	11%
General Hospital Murska Sobota	169	8%
Overall	2139	100%

Demographics

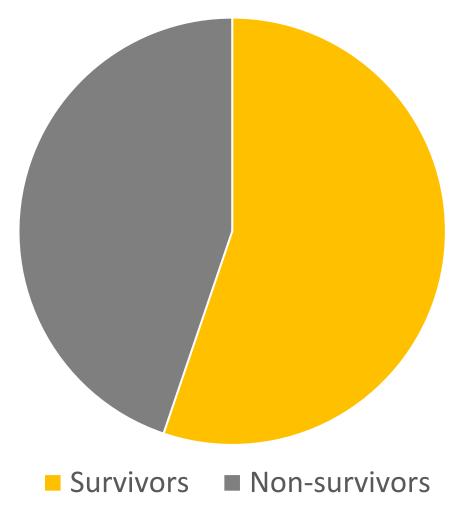
- 2139 patients
- Female: 33% (690)
- Age: median 68 years (IQR 60-75)



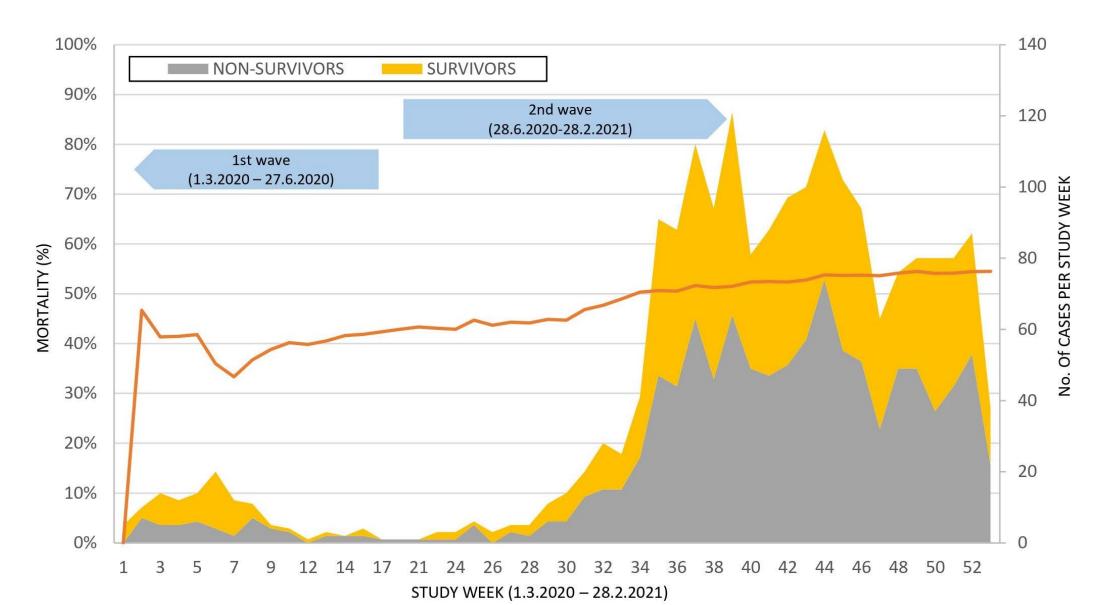
Mortality

- 55% (1181 patients)
- only 53 patients (4%) died outside ICU
 - Median time to death 6 days (IQR 3-14)
- any form of treatment limitation in 35% of non-survivors
 - withholding: 8%
 - withdrawing: 7%

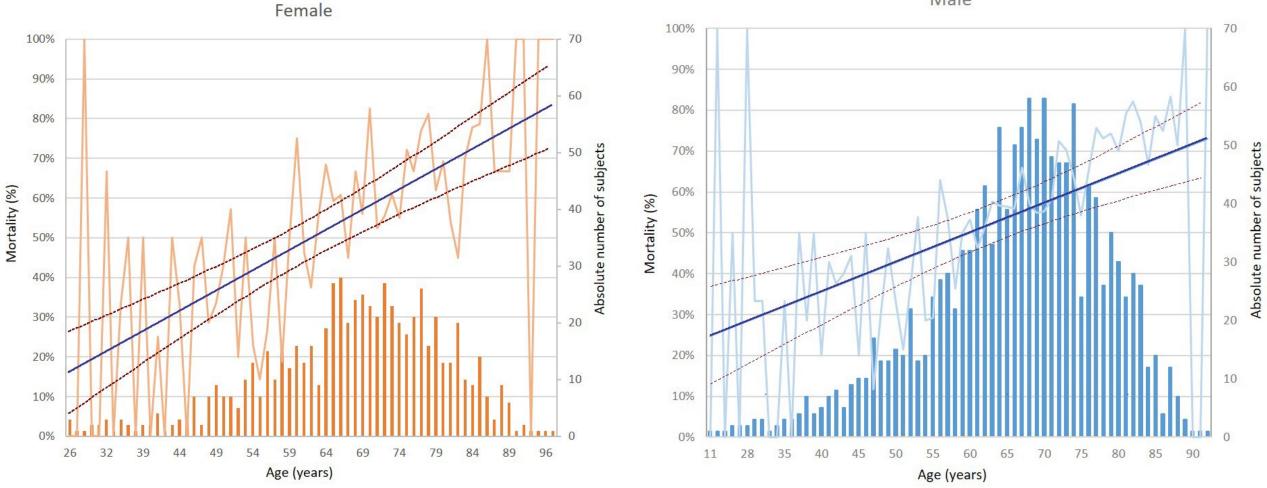
Overall in-hospital mortality



Time course of enrollment and mortality

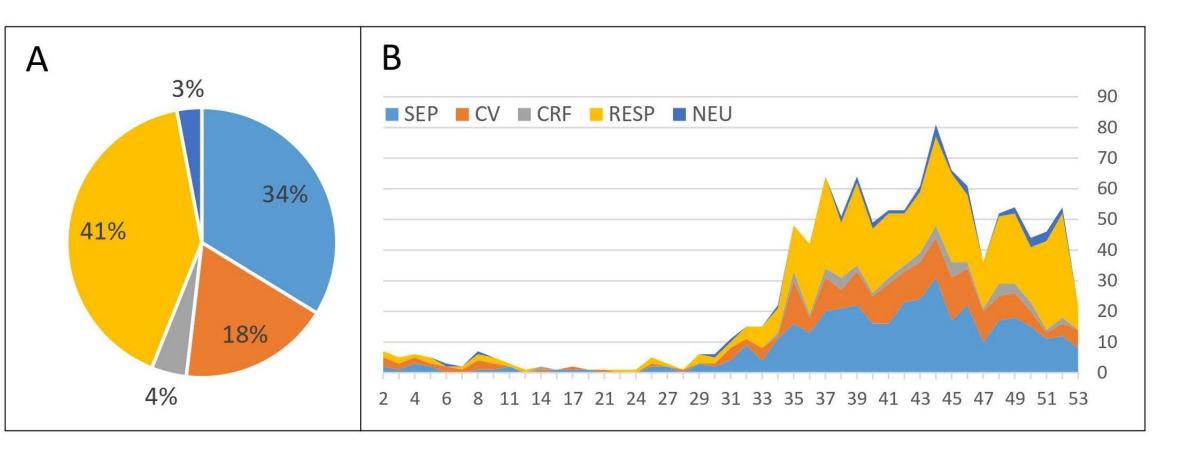


Patient distribution and mortality by gender and age groups



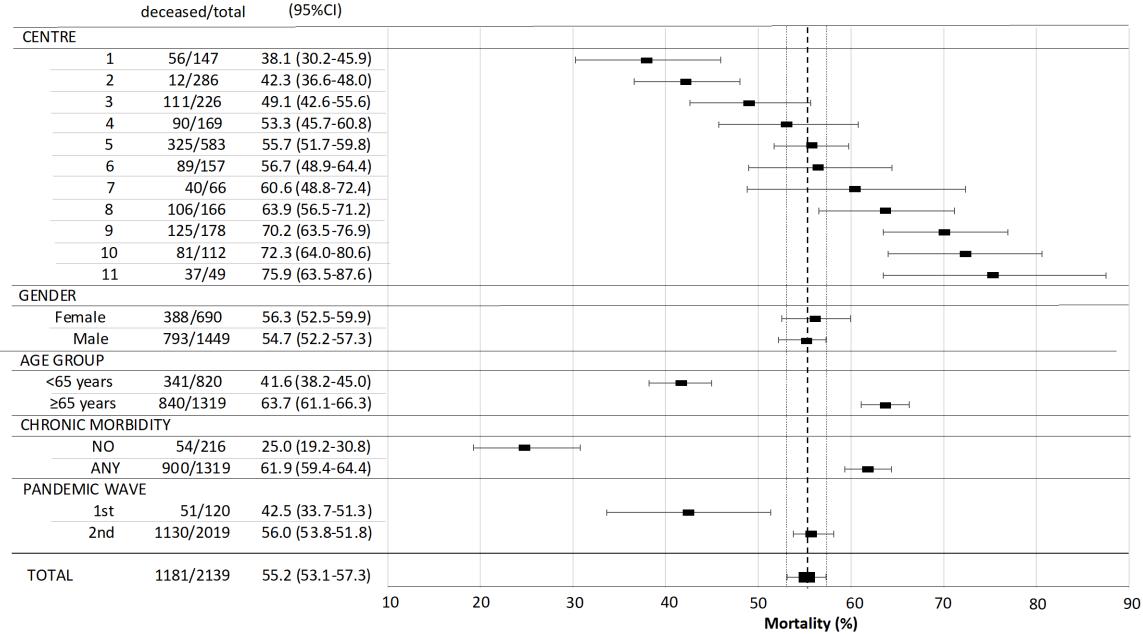
Male

Causes of death



RESP – respiratory, CV – cardiovascular, CRF – cardiorespiratory failure, SEP – sepsis, NEU - neurological

Determinants of mortality?



Mortality %

No of patients

Survivors vs. non-survivors: demographic and time describing parameters

	Overall	Survivors	Non-survivors	p-value	
	N=2139	N=958	N=1181		
Age	68 (60-75)	65 (55-72)	7 0 (64-77)	< 0.0001	
Female	690 (33 %)	302 (34 %)	388 (33 %)	NS	
BMI	30.1 (27.0-34.7)	30.7 (27.3-34.9)	30.0 (26.8-34.6)	NS	
Onset of symptoms before ICU admission (days)	6 (2-9)	6 (3-9)	5 (2-8)	<0.0001	
ICU pre-admission hospital length of stay (days)	1 (0-4)	2 (0-4)	1 (1-5)	0.023	
ICU length of stay (days)	9 (5-16)	10.5 (6-18)	8 (4-15)	< 0.0001	
Organ support free total length of stay (days)	1 (0-4)	3 (1-7)	1 (0-3)	< 0.0001	

Survivors vs. non-survivors: comorbidities

	Overall Survivors Non-survivors		Non-survivors	p-value
	N=1656	N=475	N=1181	
Without comorbidities	230 (12 %)	162 (23 %)	68 (6 %)	<0.0001
Diabetes mellitus	626 (38 %)	165 (35 %)	461 (39 %)	NS
Arterial hypertension	1201 (73%)	475 (64 %)	895 (74 %)	NS
Chronic heart disease	575 (35 %)	114 (24 %)	461 (39 %)	NS
Chronic respiratory disease	297 (18 %)	80 (17 %)	217 (18 %)	NS
Immunocompromised (including dialysis, malignancy)	450 (27 %)	91 (19 %)	359 (30 %)	NS
CPR before ICU admission	32 (2 %)	7 (1 %)	25 (2 %)	NS

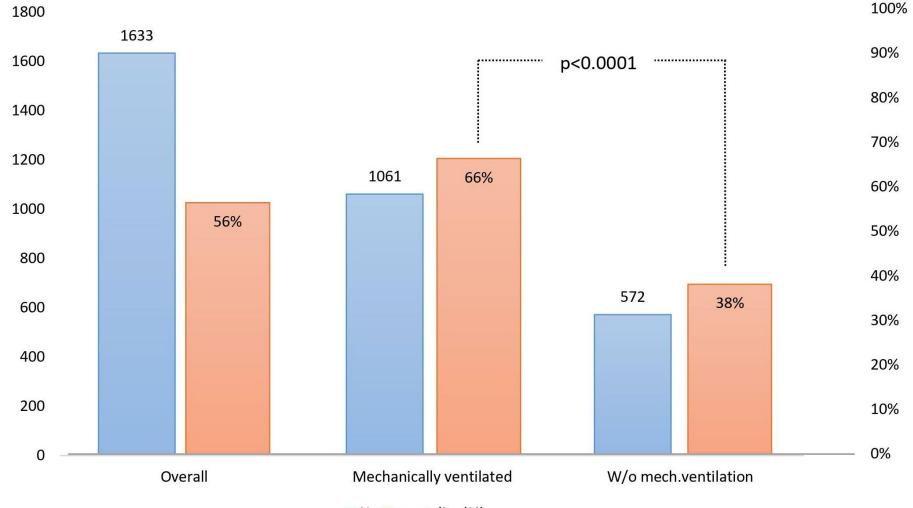
Survivors vs. non-survivors: ICU complications

	Overall	Survivors	Non-survivors	p-value
	N=1656	N=475	N=1181	
Pulmonary embolism	106 (6 %)	27 (6 %)	79 (7 %)	NS
HAP/VAP	444 (27 %)	148 (31 %)	296 (25 %)	NS
Barotrauma	32 (2 %)	5 (1 %)	27 (2 %)	NS
CPR	255 (15 %)	7 (1 %)	248 (21 %)	NS

Survivors vs. non-survivors: organ support

	Overall	Survivors	Non-Survivors	p-value
	N=1687	N=733	N=954	
Only HFNC	317 (19 %)	192 (26 %)	125 (13 %)	<0.0001
Only NIV	129 (8 %)	64 (9 %)	65 (7 %)	NS
Invasive ventilation w/o ECMO	1061 (63 %)	357 (49 %)	704 (74 %)	<0.0001
ECMO	54 (3 %)	22 (3 %)	32 (3 %)	NS
Vasopressor therapy	1093 (65 %)	365 (50 %)	728 (76 %)	<0.0001
Inotropic support	200 (12 %)	38 (5 %)	162 (17 %)	<0.0001
RRT	205 (12 %)	54 (7 %)	151 (16 %)	<0.0001

Invasive mechanical ventilation & mortality



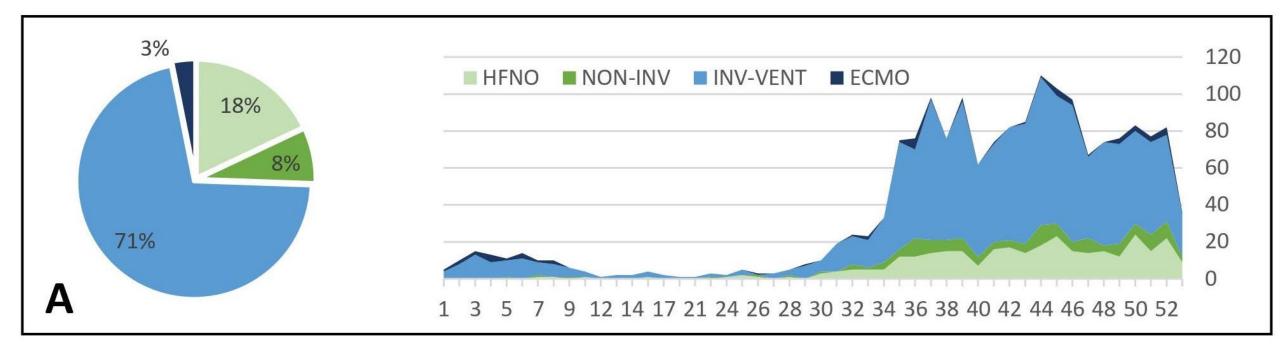
🔲 N 📒 mortality (%)

Respiratory support initial use

- HFNO: 913 pts (54.1%)
 - sufficient in 317 (35%) of pts

- NON-INV: 405 pts (24.0%)
 - escalated to INV-VENT in 276 pts (68%)
- INV-VENT from admission in 434 pts (25.7%)
 - mortality 70%
 - 109 pts (25%) died during first 24 hrs

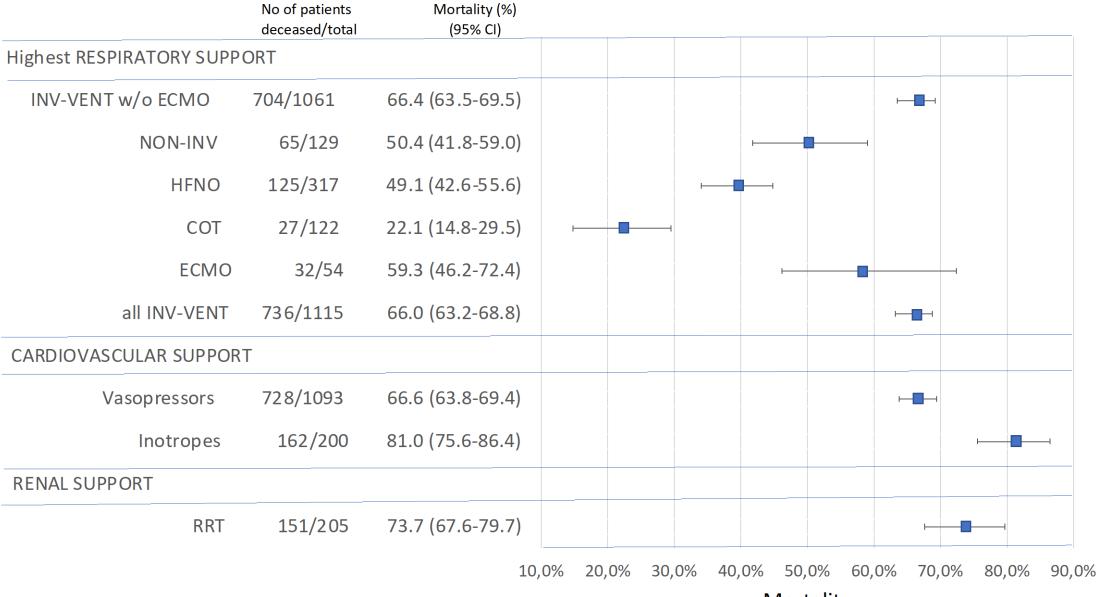
Treatment: the highest form of respiratory support



HFNO - high-flow nasal oxygen; NON-INV - non-invasive ventilation INV-VENT - invasive mechanical ventilation; ECMO - extracorporeal oxygenation

Conventional oxygen therapy (COT) excluded from the analysis

Organ support & mortality

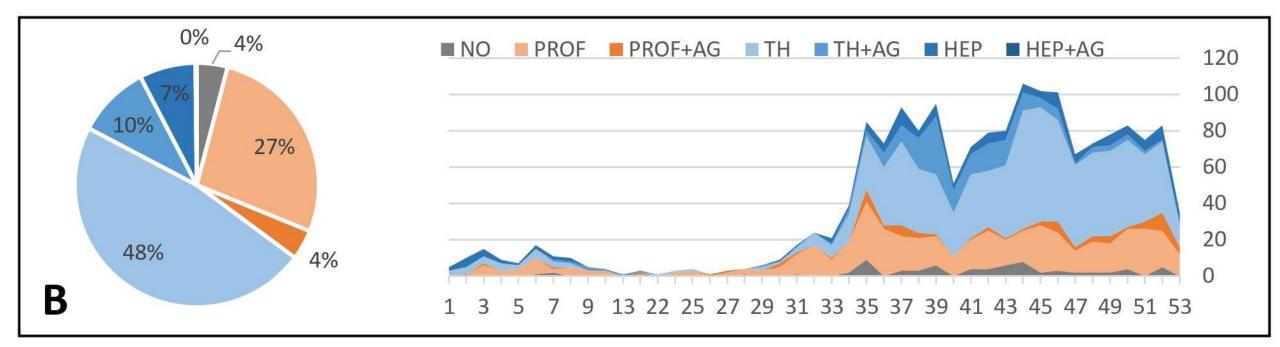


Mortality

Survivors vs. non-survivors: treatment

Specific treatments	Overall	Survivors	Non-survivors	
	N=1744	N=721	N=1023	
Corticosteroids (any dose)	1520 (87 %)	626 (87 %)	894 (84 %)	NS
Standard dose	1017 (58 %)	424 (59 %)	593 (58 %)	NS
Higher dose	503 (29 %)	202 (28 %)	301 (29 %)	NS
DVT prophylaxis	540 (31 %)	218 (30 %)	322 (31 %)	NS
Anticoagulation (heparin or high-dose LMWH)	1128 (65 %)	486 (67 %)	642 (63 %)	NS
Anti-platelets (chronic or new medication)	240 (14 %)	93 (13 %)	146 (14 %)	NS
Antivirals (any of the following)	407 (23 %)	196 (27 %)	211 (21 %)	NS
Remdesivir	264 (15 %)	145 (20 %)	119 (12 %)	NS
Lopinavir/ritornavir	15 (1 %)	8 (1 %)	7 (1 %)	NS
Favirapivir	178 (10 %)	68 (9 %)	110 (11 %)	NS

Treatment: antithrombotics



NO - no anti-thrombotics; PROF - prophylactic low-molecular weight;

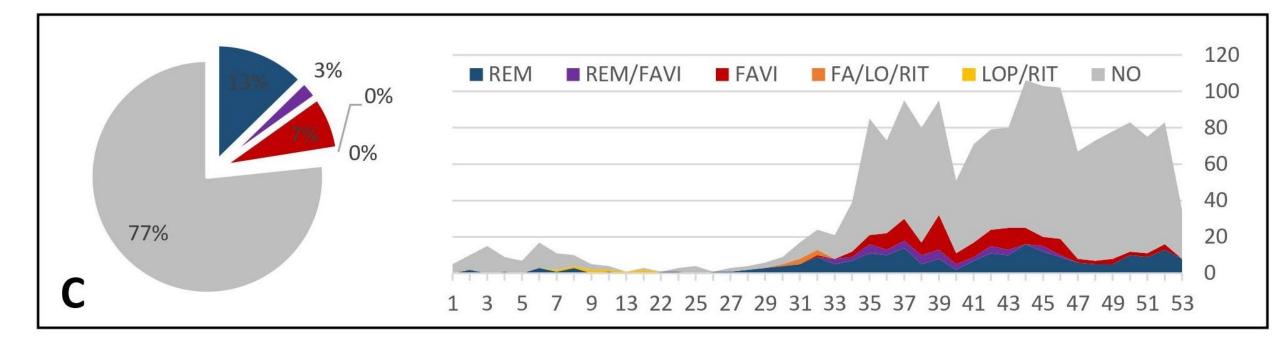
PROF+AG - prophylactic low-molecular weight heparin + anti-aggregants;

TH - therapeutic low-molecular weight heparin;

TH+AG - therapeutic low-molecular weight heparin + anti-aggregants;

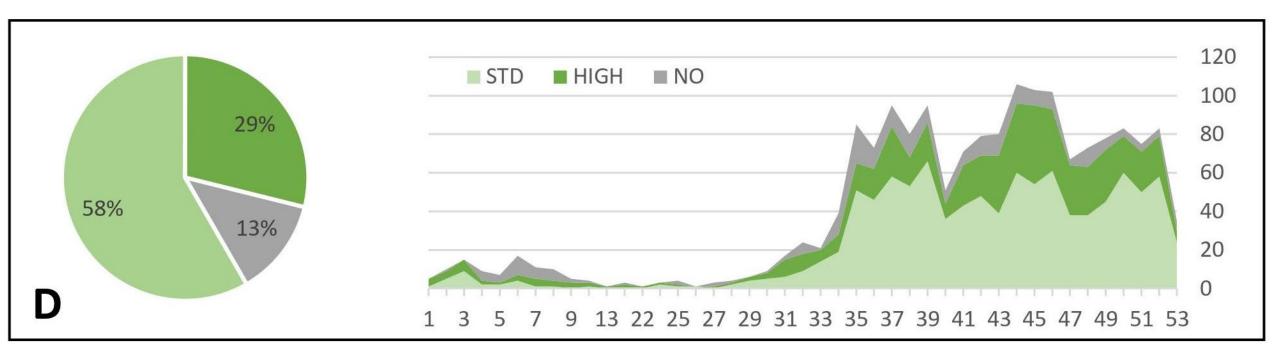
HEP - heparin anticoagulation; HEP+AG - heparin anticoagulation + anti-aggregants

Treatment: antivirals



NO - no antivirals; REM – remdesivir; FAVI - favirapivir; LOP/RIT - lopinavir-ritornavir combination

Treatment: corticosteroids



NO - without steroids; STD - standard dose of dexamethasone 6-8mg/day equivalents; HIGH - any higher dose

Survivors vs non-survivors: baseline SOFA, APACHE II, PaO₂/FiO₂ & laboratory parameters

	Overall		Survivors		Non-survivors		p-value
	Ν	Median (IQR)	Ν	Median (IQR)	Ν	Median (IQR)	
SOFA	515	7 (4-10)	156	4 (2-8)	359	8 (5-11)	<0.0001
APACHE II	551	17 (12-25)	187	13 (10-19)	364	21 (14-27)	<0.0001
PaO ₂ /FiO ₂ (mmHg)	1352	97 (66-150)	527	123 (80-200)	825	84 (62-124)	<0.0001
Lymphocyte count (10 ⁹ /L)	1286	0.46 (0.16-0.95)	424	0.70 (0.46-1.86)	862	0.32 (0.07-0.75)	<0.0001
CRP (mg/L)	1711	118 (62-190)	706	104 (54-173)	1005	128 (70-205)	<0.0001
PCT (ng/mL)	1490	0.39 (0.18-1.14)	501	0.30 (0.12-1.00)	989	0.41 (0.20-1.31)	<0.0001
IL-6 (pg/mL)	448	68 (23-144)	155	45 (15-106)	293	88 (28-191)	<0.0001
Ferritin (ųg/L)	939	1081 (580-2000)	351	797 (418-1542)	588	1311 (741-2030)	< 0.0001
D-dimers (mg/L)	1226	2.65 (1.22-9.00)	373	2.12 (1.13-7.32)	853	3.06 (1.26-10.19)	0.0083
Serum lactate (mmol/L)	1308	1.8 (1.3-2.9)	400	1.3 (1.0-1.8)	908	2.2 (1.5-3.5)	<0.0001

How we compare to others?



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COVID-19 1st wave

Case Fatality Rate (CFR)

- January 1, 2020 June 8, 2020
- 57 420 adults requiring INV-VENT
- CFR 45% (95%CI: 35%-52%)
- *Heterogeneity* (*I*² >90%)
- Europe 36% (95%CI: 24%-48%)
 - ICNARC 48% (95%CI: 47%-50%)
- Asia 47% (95%CI: 33%-62%)
- Middle East 52% (95%CI: 19%-85%)
- North America 46% (95%CI: 36%-57%)
- South America 49% (95%CI: 0%-87%)
 - Brazil registry 72% (95%CI: 71%-72%)

Study	Study size	Deaths		CFR with 95% CI	Weight (%
Asia Chen et al, May 2020	9	6		0.67 (0.40-0.93)	1.27
Hu et al, May 2020	34	31		0.91 (0.80-1.00)	1.54
Hu et al, May 2020	67	39		0.58 (0.47-0.70)	1.53
Hua et al, June 2020	113	104		0.92 (0.87-0.97)	1.59
Huang et al, June 2020	4	2		0.50 (0.15-0.85)	1.10
Japan registry, July 2020	575	133		0.23 (0.20-0.27)	1.60
Jung et al, May 2020	36	21	_t=	0.58 (0.43-0.74) 0.30 (0.05-0.55)	1.48
Liao et al, April 2020 Nasir et al, June 2020	10	3		0.30 (0.05-0.55) 0.50 (0.24-0.76)	1.29
Ratanarat et al, July 2020	10 5	5 0			1.27 1.26
Ruan et al, June 2020	25	25		0.00 (0.00-0.27) 1.00 (0.91-1.00)	1.56
Shi et al, June 2020	36	29	in tanî	0.81 (0.68-0.93)	1.51
Sirivongrangson et al, June 2020	10	0		0.00 (0.00-0.18)	1.43
Wang et al, April 2020	4	0		0.00 (0.00-0.30)	1.20
Wang et al, June 2020	50	25		0.50 (0.37-0.63)	1.51
Wang et al, March 2020	18	5		0.28 (0.08-0.47)	1.40
Yang et al, May 2020	59 22	36 19		0.61 (0.49-0.73)	1.52
Yang et al, May 2020 Ye et al, June 2020	22	19		0.86 (0.71-1.00) 0.03 (0.00-0.13)	1.48
Young et al, March 2020	1	ò		0.00 (0.00-0.44)	0.93
Yu et al, May 2020	121	79		0.65 (0.57-0.74)	1.57
Zhao et al, June 2020	5	1		0.20 (0.00-0.51)	1.18
Zheng et al, May 2020	15	0		0.00 (0.00-0.14)	1.50
Zhu et al, June 2020	29	25		0.86 (0.73-0.99)	1.51
Heterogeneity: T ² = 0.11, I ² = 97.12%, H ² = 34.74 Test of θ = Q (23) = 951.46, p = 0.00			•	0.47 (0.33-0.62)	
Middle East					
Almazeedi et al, May 2020	31	13		0.42 (0.26-0.58)	1.46
Goshayeshi et al, May 2020	231	81		0.35 (0.29-0.41)	1.58
Khamis et al, July 2020	16	5	-==+	0.31 (0.10-0.52)	1.38
Rinott et al, June 2020	17 2	12 2		0.71 (0.50-0.91)	1.39
Shahriarirad et al, June 2020	2	2	A	1.00 (0.62-1.00) 0.52 (0.19-0.85)	1.04
Heterogeneity: $T^2 = 0.05$, $I^2 = 88.04\%$, $H^2 = 8.36$ Test of $\theta = 0.04$ = 21.46, $\theta = 0.00$				0.02 (0.13-0.03)	
Test of $\theta = Q$ (4) = 21.46, p = 0.00					
Europe			_	/	
Alfano et al, June 2020 Rugette et al. May 2020	53	17		0.32 (0.20-0.44)	1.52
Busetto et al, May 2020 Ceruti et al, May 2020	9 34	0 7		0.00 (0.00-0.20) 0.21 (0.07-0.34)	1.40 1.50
Ceruti et al, May 2020 France registry, June 2020	34 2357	480		0.20 (0.19-0.22)	1.61
Giacomelli et al, May 2020	8	7		0.88 (0.63-1.00)	1.31
Grasselli et al, April 2020	1150	329		0.29 (0.26-0.31)	1.60
ICNARC, July 2020	7185	3479	₩	0.48 (0.47-0.50)	1.61
Israelsen et al, May 2020	27	17		0.63 (0.46-0.80)	1.45
Pavoni et al, May 2020 Redemen et al, April 2020	4	3		0.75 (0.41-1.00)	1.12
Pederson et al, April 2020 Piano et al, June 2020	17	7	-	0.41 (0.20-0.62) 0.29 (0.18-0.40)	1.37
Regina et al, May 2020	62 38	18 11	- -	0.29 (0.15-0.43)	1.54 1.50
Spain registry, July 2020	3867	1943		0.50 (0.49-0.52)	1.61
Sweden registry, July 2020	2412	455		0.19 (0.17-0.20)	1.61
Zangrillo et al, April 2020	73	17	-	0.23 (0.14-0.33)	1.55
Heterogeneity: $T^2 = 0.04$, $I^2 = 99.39\%$, $H^2 = 163.58$ Test of $\theta = Q(14) = 1663.54$, $p = 0.00$			•	0.36 (0.24-0.48)	
North America					
Aggarwal et al, May 2020	5	0		0.00 (0.00-0.27)	1.26
Arentz et al, March 2020	15	10		0.67 (0.45-0.88)	1.36
Argenziano et al, May 2020	233	111		0.48 (0.41-0.54)	1.58
Auld et al, May 2020 Rhatraiu et al, March 2020	165 18	56 9		0.34 (0.27-0.41) 0.50 (0.29-0.71)	1.58
Bhatraju et al, March 2020 Buckner et al, May 2020	18 19	9 10		0.53 (0.32-0.73)	1.39
Buckner et al, May 2020 Ferguson, et al, July 2020	19	10 3		0.23 (0.32-0.73)	1.39 1.36
Garibaldi et al, May 2020	70	24	-	0.34 (0.23-0.45)	1.54
Gold et al, May 2020	92	38	+	0.41 (0.31-0.51)	1.55
Goyal et al, April 2020	130	19		0.15 (0.08-0.21)	1.58
Klang et al, May 2020	809	682		0.84 (0.82-0.87)	1.60
Mani et al, July 2020	30	13		0.43 (0.27-0.60)	1.45
Mexico registry, July 2020	6898	4724	_ 1 =	0.68 (0.67-0.70)	1.61
Mitra et al, June 2020	74	15		0.20 (0.11-0.29)	1.56
Palaiodimos et al, July 2020 Petrilli et al, May 2020	42 647	32 391		0.76 (0.63-0.89) 0.60 (0.57-0.64)	1.51
Petrilli et al, May 2020 Reyes Gil et al, May 2020	55	391		0.82 (0.72-0.92)	1.60 1.55
Richardson et al, April 2020	1151	282		0.25 (0.22-0.27)	1.60
Salacup et al, July 2020	54	38		0.70 (0.58-0.82)	1.53
Shekar et al, May 2020	22	12	_+=-	0.55 (0.35-0.74)	1.41
Shi et al, July 2020	61	16	=	0.26 (0.15-0.07)	1.54
Suleyman et al, June 2020	114	91		0.80 (0.45-1.00)	1.11
Ziehr et al, June 2020	66	11		0.17 (0.08-0.26)	1.56
Heterogeneity: T ² = 0.05, I ² = 98.71%, H ² = 77.62 Test of θ = Q (22) = 1936.42, p = 0.00			T	0.46 (0.36-0.57)	
South America	077.40	10005			
Brazil registry, July 2020	27748 9	19935		0.72 (0.71-0.72)	1.61
Olivares et al, June 2020	9	2		0.22 (0.00-0.47)	1.30
Heterogeneity: $T^2 = 0.11$, $I^2 = 93.29\%$, $H^2 = 14.90$ Test of $\theta = Q$ (1) = 14.90, p = 0.00				0.49 (0.00-0.97)	
Overall			•	0.45 (0.39-0.52)	
Heterogeneity: T ² = 0.07, I ² = 99.52%, H ² = 208.86			Ţ		
Test of $\theta = Q$ (68) = 11173.01, p = 0.00					
			1		
Random effects REML model					
Random effects REML model			0.5 1		

Mortality in other studies of ICU patients

- Italy: ICU mortality in Lombardy 25% (Graselli et al., JAMA 2020) and 37% in invasively ventilated pts from COVID-19 Italian ICU Network (Zanella et al. Intensive Care Med. 2021)
- UK (ICNARC): overall mortality 50.2% (1st wave) and 35.2% (2nd wave)
- **Germany**: slightly >50% in invasively ventilated pts during 1st and 2nd wave (Karagiannidis et al. Lancet Respir Med. 2021)
- SEMICYUC Working Group (Andora, Ireland and Spain, n= 3795): overall mortality 31.7% (1st wave) and 28.8% (2nd wave) (Carbonell et al.. Lancet Reg Health Eur. 2021)
- The Euroregio Meuse-Rhine (7 ICUs, n= 551): overall mortality 22% in Belgium, 42% in The Netherlands and 44% in Germany during 1st wave (Mesotten et al. Crit Care Med 2022)
- Poland: small cohort (n=32) from Tychy: overall mortality 67% (Kokoszka-Bargiel et. al. Med Sci Monitor 2021); bigger cohort (n=286) from Wrocław: overall mortality 68% (Czapla et. al. Nutrients 2021)
- **Croatia**: small cohort (n=30) from Zagreb: invasively ventilated pts mortality **67%** (Gjurasin et. al. Wien Clin Wochenschr 2021)
- **Russia** (n=1522): overall mortality **65.4%** (Moiseev et al. Anaesthesia 2021 [letter])

Eur J Anaesthesiol 2023; 40:4-12

ORIGINAL ARTICLE

Clinical characteristics and factors associated with ICU mortality during the first year of the SARS-Cov-2 pandemic in Romania

A prospective, cohort, multicentre study of 9000 patients

Şerban-Ion Bubenek-Turconi^{*}, Stefan Andrei^{*}, Liana Văleanu^{*}, Mihai-Gabriel Ștefan^{*}, Ioana Grigoraș, Sanda Copotoiu, Constantin Bodolea, Dana Tomescu, Mihai Popescu, Daniela Filipescu, Horatiu Moldovan, Alexandru-Florin Rogobete, Cosmin Bălan, Bianca Moroșanu, Dorel Săndesc and Raed Arafat, COVATI-RO Collaborative[†]

KEY POINTS

- This study analysed data from a large national European cohort, which to our knowledge, is the largest published Eastern European cohort of critically ill patients.
- Older age, male gender, neoplasia, chronic kidney disease, diabetes, chronic heart failure, clinical severity on ICU admission, the necessity for noninvasive or invasive ventilation were the factors associated with higher ICU mortality.
- Treatment with tocilizumab and hydroxychloroquine were associated with improved survival.

- Overall mortality 62%
- Maximal SOFA 6 (median)
- Mechanical ventilation in 49% of pts
 - 9.6% of survivors and 73.3% of non-survivors

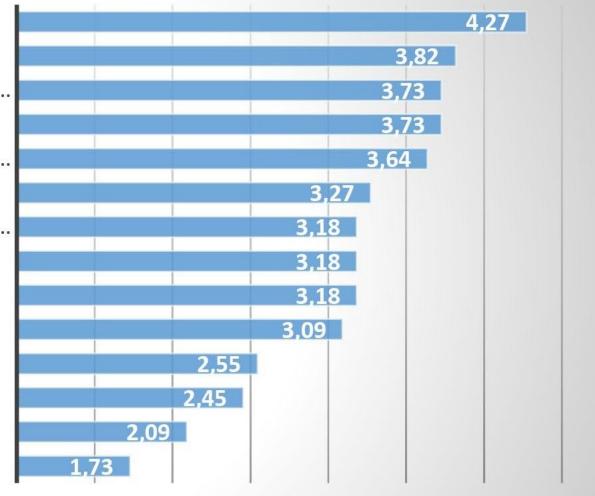
Factors subjectively associated with unfavourable outcome

1,00

1,50

2,00

2,50



3,50

3,00

4,00

4,50

5,00

LACK OF SPECIALISED NURSES LACK OF INTENSIVISTS EXTREMELY HIGH RATE OF ADMISSIONS WITHIN A VERY. LACK OF PERSONNEL IN GENERAL THE DISEASE ITSELF WAS DEADLY - NO OTHER... LATE ADMISSION TO ICU LACK OF COMMUNICATION (CENTRES, HEALTH... LATE REFERRAL TO ICU **POOR INFRASTRUCTURE OF THE COVID ICUS*** POOR INFRASTRUCTURE IN GENERAL LACK OF EQUIPMENT (VENTILATORS, ECMO, PUMPS, ETC.) LACK OF "NOT FIT FOR ICU" DECISIONS LACK OF FOLLOWING INTERNATIONAL GUIDELINES LACK OF DRUGS (TOCILIZUMAB, STEROIDS, ETC.)

Conclusions

- We present comprehensive COVID-19 dataset from Central-Eastern European ICUs suggesting the potential high mortality rate observed especially in those receiving invasive mechanical ventilation.
- There is still a plausible difference in quality of health care and research output between the East and West that has not changed for almost two decades since our joining the European Union.
- Our results render the need of a paradigm change in Central-Eastern Europe to establish high quality, structured data collection and to improve research facilities and output, all contributing to better patient outcomes in Central-Eastern Europe.

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