Supplemental Material

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Supplementary Methods

Covid-19 diagnostic tool and hospitalization criteria

The most common Covid-19 diagnostic tool at admission was the nasopharyngeal swab, with a PCR performed in 824 patients (98%). Bronchoalveolar washing was performed in 7 patients (1%) and 8 patients had a blood test with positive antibody (1%).

The hospitalization criteria for Covid-19 patients were determined according to the WHO guidelines (having a pneumonia with CURB-65 ≥ 2, oxygen dependency, tachypnea (≥20/min), any organ failure, and altered conscious status).[1] Criteria for the intensive care unit admission were followed according to the Swiss Medical Society of Intensive Care Medicine.[2]

Study definitions

CV risks factors were defined as: hypertension, obesity (based on patients' records of their height and weight and defined as body mass index (BMI) ≥30 kg/m^2, dyslipidemia, diabetes (type I or type II), active smoking, physical inactivity, stress, family history of CVD and familial hypercholesterolemia.

Comorbidities were determined as follows: myocardial infarction (MI), either ST Elevation MI (STEMI), non ST Elevation MI (NSTEMI), unstable angina (UA), stable angina, were defined according to the international guidelines.[3] Myocarditis was defined at the cardiac MRI with evidence of myocardial inflammation, according to the guidelines.[4] Pericarditis was defined as inflammation to the pericardium with associated symptoms, according to the European guidelines. [5] Heart failure, transthoracic echocardiography with left ventricle ejection fraction < 50 %, heart failure symptoms and elevated NT-pro BNP according to the European guidelines.[6]

Peripheral artery disease was defined as narrowed arteries with reduced blood flow to the limbs, according to the European guidelines.[7]

Moderate or severe chronic kidney failure were defined when GFR (Glomerular Filtration Rate) was between 59 and 30 mL/min/1.73m^2 and <30 mL/min/1.73m^2 , respectively.[8]

Venous thrombotic complications included: pulmonary embolism, portal vein thrombosis and deep vein thrombosis.

Statistical analysis: complementary information

Patients' characteristics were described overall and according to clinical status at discharge (survived, survived but MACE, dead). Qualitative parameters were compared between the three groups using chi-square test or Fisher's exact test, whilst age was compared between groups using Kruskal-Wallis test.

Primary and secondary outcomes were described and compared according to the history of CVD: composite outcome, vital status, MACE and its components, ICU admission, IMCU admission and admission to a rehabilitation care unit were compared between patients without history of CVD and patients with history of CVD using a chi-square test or a Fisher's exact test. Total length of stay, Intensive Care Unit (ICU) length of stay, Intermediate Care Unit (IMCU) length of stay and rehabilitation length of stay were compared between the two groups using Welch Student test.

Laboratory values measured at admission were compared between groups according to clinical status at discharge (survived, survived but MACE, dead) using Kruskal-Wallis test.

Treatment at admission was compared between groups according to the primary composite outcome (discharge alive with no MACE vs. MACE and/or death). Crude and age-adjusted OR were estimated using logistic regression model to assess associations between medication at admission and the primary composite outcome.

Supplemental Material Table 1: Laboratory values at admission

Lab value (n)	All patients (n=839)	Survived (n=615)	Survived with MACE (n=72)	Died (n=152)	P value
Urea (817)	5.3 (3.8 - 7.8)	4.6 (3.4 - 6.4)	7.8 (5.7 - 10.6)	8.4 (5.8 - 13.9)	<0.001
Thrombocytes (815)	195 (152 - 248)	197 (157 - 247)	204 (157 - 266)	186 (134 - 246)	0.09
Sodium (817)	136 (134 - 139)	136 (134 - 139)	136 (133 - 139)	137 (133 - 140)	0.31
Leucocytes (814)	5.9 (4.4 - 8)	5.7 (4.3 - 7.5)	6.2 (4.8 - 8.1)	7.2 (4.9 - 10.4)	<0.001
Lymphocytes (748)	0.9 (0.6 - 1.3)	1 (0.7 - 1.4)	0.9 (0.6 - 1.2)	0.7 (0.5 - 1)	<0.001
Potassium (807)	3.9 (3.6 - 4.2)	3.9 (3.6 - 4.1)	4.1 (3.7 - 4.5)	4 (3.6 - 4.5)	<0.001
Haemoglobin (814)	133 (120 - 145)	136 (125 - 147)	124 (110 - 141)	121 (103 - 137)	<0.001
Erythrocytes (815)	4.5 (4 - 4.9)	4.6 (4.2 - 5)	4.3 (3.6 - 4.7)	4 (3.4 - 4.6)	<0.001
CRP (804)	54 (22 - 97)	50 (20 - 91)	51 (13 - 82)	78 (41 - 148)	<0.001
Creatinine (817)	80 (65 - 105)	76 (63 - 95)	98 (79 - 126)	108 (76 - 157)	<0.001
ALT (779)	30 (21 - 46)	31 (23 - 50)	28 (17 - 37)	24 (17 - 40)	<0.001
AST (767)	39 (28 - 57)	39 (28 - 57)	35 (25 - 48)	45 (30 - 67)	0.02
AST/ALT (767)	1.3 (1 - 1.7)	1.2 (1 - 1.5)	1.4 (1.1 - 2)	1.7 (1.3 - 2.2)	<0.001

CRP: C reactive protein, ALT: Alanine Transaminase, AST: Aspartate Transaminase.

Values are all median (Q1-Q3)

All P values are according to Kruskal-Wallis test.

Unit of measure: Urea (mmol/l), Thrombocytes (G/l) Sodium (mmol/l) Leucocytes (G/l) Lymphocytes (%), Potassium (mmol/l) Haemoglobin (g/l), Erythrocytes (T/l), CRP (mg/l), Creatinine (µmol/l), ALAT (U/l), ASAT (U/l).

Supplemental Material Table 2: Medication at admission and composite outcome

Medication at admission	No event (n=615)	Composite outcome (n=224)	Crude OR [95%CI]	Age-adjusted OR [95%CI]	P value
Statin	119 (19%)	74 (33%)	2.06 [1.46 to 2.89]	1.25 [0.85 to 1.82]	0.26
Antiaggregant	109 (18%)	70 (31%)	2.11 [1.48 to 2.99]	1.12 [0.76 to 1.65]	0.57
ARBs	106 (17%)	60 (27%)	1.76 [1.22 to 2.52]	1.24 [0.83 to 1.85]	0.3
Betablocker	69 (11%)	77 (34%)	4.14 [2.86 to 6.03]	2.34 [1.55 to 3.53]	<0.001
Calcium-channel blocker	62 (10%)	47 (21%)	2.37 [1.56 to 3.58]	1.61 [1.01 to 2.58]	0.05
Loop Diuretics	43 (7%)	65 (29%)	5.44 [3.57 to 8.35]	2.57 [1.62 to 4.1]	<0.001
Thiazide Diuretics	74 (12%)	31 (14%)	1.17 [0.74 to 1.83]	0.86 [0.52 to 1.39]	0.54
Anticoagulant	47 (8%)	48 (21%)	3.3 [2.13 to 5.11]	1.43 [0.88 to 2.32]	0.14
ACE inhibitor	59 (10%)	35 (16%)	1.75 [1.1 to 2.72]	1.19 [0.72 to 1.95]	0.5

ARBs: Angiotensin II Receptors Blockers, ACE inhibitor: Angiotensin Converting Enzyme Inhibitor.

Definition of categories

- In the category of statins, all of the following were included: simvastatin, rosuvastatin, atorvastatin, any other statin.
- In the category of antiaggregants, all of the following were included: aspirine, tocagrelor, prasugrel, clopidogrel.
- In the category of ARBs, all of the following were included: olmesartan, valsartan, losartan, irbesartan, candesartan, telmisartan.
- In the category of beta-blockers, all of the following were included: metoprolol, carvedilol, bisoprolol, atenolol, propanolol.
- In the category of calcium channel blockers, all of the following were included: amlodipine, nifedipine, felopidine, verapamil, diltiazem.

- In the category of loop diuretic, all of the following were included: torasemide, furosemide, bumetanide, piretanide.
- In the category of thiazide diuretics, all of the following were included: indapamide, hydrochlorotiazide, chlortalidone.
- In the category of anticoagulants, all of the following were included: rivaroxaban, dabigatran, apixaban, edoxaban, sintrom.
- In the category of ACE-inhibitors, all of the following were included: ramipril, enalapril, lisinopril, perindopril, captopril.

Supplemental Material Table 3: Sensitivity analysis

	Composite outcome (n=216/759)		Death (n=133/681)	
	Adjusted OR [95%CI]	**P value**	**Adjusted OR [95%CI]**	**P value**
History of CV disease	2.4 [1.6 to 3.6]	<0.001	3.2 [1.9 to 5.6]	<0.001
Age (per 10 years)	2.2 [1.9 to 2.7]	<0.001	2.5 [2.0 to 3.3]	<0.001
Male Sex	1.6 [1.1 to 2.4]	0.02	1.8 [1.1 to 3.1]	0.02
Lung opacity/infiltration	1.9 [1.2 to 3.0]	0.01	2.8 [1.6 to 4.9]	<0.001
Hypertension	0.82 [0.53 to 1.2]	0.35	0.85 [0.49 to 1.5]	0.55
Obesity (BMI≥30) (n=759)	1.5 [0.92 to 2.4]	0.11	1.7 [0.91 to 3.1]	0.09
Dyslipidemia	0.85 [0.55 to 1.3]	0.44	0.70 [0.41 to 1.2]	0.18
Diabetes	1.4 [0.85 to 2.2]	0.19	1.5 [0.82 to 2.6]	0.19
Smoking	1.6 [0.65 to 3.7]	0.29	1.3 [0.37 to 4.2]	0.63
COPD	2.0 [0.98 to 4.0]	0.06	2.0 [0.87 to 4.4]	0.10
Obstructive Sleep Apnea	1.2 [0.64 to 2.3]	0.53	1.2 [0.52 to 2.6]	0.69
High Creatinine* (n=817)	-		1.1 [0.63 to 1.8]	0.82
CRP (per 10 unit) (n=804)	-		1.11 [1.07 to 1.15]	<0.001
Anemia † (n=814)	-		1.4 [0.82 to 2.3]	0.22
AST/ALT>1 (n=767)	-		1.6 [0.79 to 3.5]	0.21

CV: cardiovascular, CRP: C reactive protein (mg/l), ALT: Alanine Transaminase (U/l), AST: Aspartate Transaminase (U/l). COPD: chronic obstructive pulmonary disease.

* Defined as creatinine>80 µmol/l for females and creatinine>106 µmol/l for males

† Anaemia defined as haemoglobin <120 g/L for women and haemoglobin <140g/L for men.

Covid-19 treatment protocol during hospitalization

A standardized Covid-19 protocol was established by our institution and was applied to all patients hospitalized for Covid-19 and who presented specific severity criteria.[9] Medications administered were: lopinavir 200 mg / ritonavir 50 mg 2 cp twice a day during 5 days and hydroxychloroquine 600 mg once during hospitalization, unless contraindications to those medications were present. (Contraindications to these treatments included long QT interval on ECG).

In cases of severe ARDS secondary to Covid-19 pneumonia, requiring intubation with ≥ 7 days since the onset of symptoms, a multidisciplinary discussion for each case was held for eligibility to receive anakinra treatment (antagonist of the interleukin-1 receptor), if not neutropenia, if normal kidney function and not increased procalcitonin or suspicion of bacterial infection.

Based on institutional protocol, 31% of patients received lopinavir / ritonavir (Kaletra) and 36% hydroxychloroquine as in-hospital treatment. Patients with CVD were less frequently prescribed lopinavir / ritonavir (19%) as well as hydroxychloroquine (24%) as compared to those without CVD, respectively 38% and 42%. This was probably due to contraindications of these two treatments in patients with known CVD, as well as interactions with other medications and to electrolyte abnormalities. Azithromycin was prescribed in 6% of all patients. Those with a history of CVD were less likely to receive azithromycin (4%) as compared to those without a history of CVD (8%), probably because of the well-known potential risk of the QT prolongation by this drug. Nevertheless only 2% of overall patients presented a long QT interval (≥500 ms) at admission's ECG. Contraindications to these treatments included long QT interval on ECG.

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