A possible benefit from therapeutic anticoagulation in patients with coronavirus disease 2019: the Dolo hospital experience in Veneto, Italy

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Introduction The pandemic of coronavirus disease 2019 (COVID-19) instantly and profoundly changed cardiology practice worldwide, with a 50% decrease in hospital admissions due to acute myocardial infarction, heart failure, and atrial fibrillation,[1] generally attributed to people's fear of the infection. However, it may also be the consequence of a dramatic fall in air pollution during lockdown as this could have indirectly benefitted the heart, that is, representing "the best possible result achieved for the worst possible reason."[2] An organizational review also led to the extensive use of lung ultrasound by cardiologists, a technique that has already been employed to detect pleural effusion and pulmonary congestion with B-lines.[3] This approach is now ideally suited for monitoring lung involvement in patients with COVID-19. Lung ultrasound frequently detects pleural line abnormalities, B-lines, and consolidation,[4] and helps avoid radiation exposure, logistic discomfort, and risk of spreading the infection through chest computed tomography. An increase in COVID-19 cases also led to the development of intermediate care units (IMCUs) for patients requiring hospital care but not meeting the severity criteria for the admission to the intensive care unit.[5] In this study, we aim to describe the first month's experience in an IMCU in Veneto, Italy.

Methods In a retrospective single-center case series, we analyzed 115 patients with confirmed COVID-19 diagnosis through nasal swabs in the emergency room and direct admission to the IMCU at Dolo Hospital, Venice, from March 13 to April 13, 2020. After the IMCU, survivors were directly discharged home (n = 80) or referred to the department of infectious diseases for clinical improvement with persistent positivity (n = 5) or sent to the ICU for mechanical ventilation (n = 30).

The follow-up was completed on April 30, 2020. The analysis began on May 1, 2020. The study group was not included in any previously published series. Patients were treated with oxygen administration (when oxygen saturation in room air was <94%) plus combination of antiviral lopinavir and ritonavir (n = 74), corticosteroid (n = 25), chloroquine (n = 85, at a dose of 450 mg twice daily), or hydroxychloroquine (n = 20, at a dose of 400 mg twice daily), and anti-inflammatory monoclonal antibody targeting interleukin 6 receptor (tocilizumab, n = 10). Oral anticoagulants were used at therapeutic doses (warfarin, n = 3, or direct oral anticoagulants, n = 10 for known atrial fibrillation) or heparin (enoxaparin, n = 35, daily doses of ≥8000 IU) or at preventive prophylactic doses (fondaparinux, n = 19, 2.5 mg daily, or enoxaparin, n = 45, 2000 to 6000 IU). Patients on oral anticoagulants prior to hospitalization were continued on the same therapy during hospitalization. Patients with no therapy were started on heparin either at low preventive (in the early days of experience) or at high therapeutic doses.

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TABLE 1 Study population

Parameter	All patients (n = 115)	Nonsurvivors (n = 19)	Survivors (n = 96)	*P* value
Age, y, median (IQR)	69 (55–78)	75 (70–82)	64 (55–77)	0.01
Male sex	78 (67.8)	16 (84.2)	62 (64.6)	0.09
Hospital stay, d, median (IQR)	13 (10–18)	11 (8–14)	14 (10–18)	0.08
Diabetes	17 (14.8)	8 (42.1)	9 (9.4)	<0.001
Hypertension	47 (40.9)	12 (63.2)	35 (36.5)	0.04
Chronic AF	15 (13)	2 (10.5)	13 (13.5)	0.72
Known CAD	4 (3.5)	0	4 (4.2)	0.37
Hemoglobin, g/dl, mean (SD)	13.36 (2.08)	12.72 (2.76)	13.49 (1.91)	0.14
Creatinine, mg/dl, median (IQR)	0.98 (0.78–1.17)	1.06 (0.84–1.36)	0.95 (0.77–1.11)	0.01
Procalcitonin, ng/ml, median (IQR)	0.1 (0.06–0.28)	0.44 (0.1–0.62)	0.1 (0.06–0.23)	0.01
Troponin T, ng/l, median (IQR)	16 (12–36)	49 (22.3–81.3)	14 (11–31)	<0.001
Pro-BNP, pg/ml, median (IQR)	241 (88–721)	1 644 (111–3 600)	227 (82–528)	0.03
D-dimer, ng/ml, day 1, median (IQR)	926 (505–1751)	1 350 (754–2401)	829 (459–1596)	0.08
D-dimer, ng/ml, day 3, median (IQR)	1226 (555–4567)	2148 (1178–6067)	1093 (487–3137)	0.03
D-dimer, ng/ml, day 6, median (IQR)	1562 (734–5534)	1718 (1562–20 138)	1175 (670–5348)	0.045
D-dimer, ng/ml, last day, median (IQR)	915 (433–2408)	3468 (1037–7516)	760 (383–1714)	<0.001
CRP, mg/l, median (IQR)	71.1 (33.9–120.9)	86.1 (56.1–131.2)	68.7 (32.3–120.8)	0.38
Albuminuria[a]	44 (38.3)	15 (78.9)	29 (30.2)	<0.001
Heparin	99 (86.1)	18 (94.7)	81 (84.4)	0.23
Heparin, high dose[b]	35 (30.4)	3 (15.8)	32 (33.3)	0.08
NOAC / VKA	13 (11.3)	0	13 (13.5)	0.09
Chloroquine or hydroxychloroquine	105 (91.3)	17 (89.5)	88 (91.7)	0.76
Antiviral agents	74 (64.3)	10 (52.6)	64 (66.7)	0.24
Antibiotics	100 (87)	18 (94.7)	82 (85.4)	0.27
Tocilizumab	10 (8.7)	0	10 (10.4)	0.14
Therapeutic anticoagulation	48 (41.7)	3 (16.7)	45 (47.9)	0.02
Prophylactic anticoagulation	64 (55.7)	15 (83.3)	49 (52.1)	0.02
ICU admission	30 (26.1)	19 (100)	11 (11.5)	<0.001

Data are presented as number (percentage) unless otherwise indicated.

a Albuminuria was defined as albumin in the urine >300 mg/g of creatinine
b Heparin high dose is a daily dose of ≥8000 IU

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CRP, C-reactive protein; ICU, intensive care unit; NOACs, non–vitamin K antagonist oral anticoagulants; pro-BNP, pro-B-type natriuretic peptide; VKA, vitamin K antagonists

This is a retrospective analysis of a clinical experience and follows the general ethical principles of transparence, sharing of data, and sharing of benefits under exceptional circumstances.[6] The institutional review board did not meet during the COVID-19 pandemic and written informed consent was given by all study participants.

Statistical analysis Categorical data were expressed as the number of patients and percentage while continuous data were presented as mean (SD) for normally distributed data or median (interquartile range [IQR]) for data with other distribution. The χ^2 test with the Fisher exact test were used to compare the distribution of categorical variables among groups. The *t* test for unpaired values was used for comparison of continuous normally distributed data. The Mann–Whitney test was used to compare nonnormally distributed data. Multivariable factors associated with death were investigated using a logistic regression model.

The multivariable model was selected using a forward approach. Odds ratios (ORs) with corresponding 95% CIs were estimated. Statistical significance was set at P value of less than 0.05. The Statistical Package for the Social Sciences (SPSS 22.0 Inc., Chicago, Illinois, United States) was adopted for the analysis.

Results and discussion A total of 19 patients died (Group 1, unfavorable outcome) while 96 were discharged alive (Group 2, favorable outcome). Patients with unfavorable outcome were more often older men, with diabetes or hypertension, with high values of D-dimer, pro-B-type natriuretic peptide, creatinine or albuminuria and without therapeutic anticoagulation (TABLE 1). In multiple regression analysis, independent predictors of death (Group 1 vs Group 2) were: age (OR, 1.109; 95% CI, 1.029–1.194; P = 0.007), D-dimer on the last day (OR, 1.000; 95% CI, 1.000–1.001; P = 0.006), and albuminuria (OR, 11.612; 95% CI, 2.142–62.963; P = 0.04). Therapeutic anticoagulation was an independent predictor of survival (oral anticoagulants or heparin dose ≥8000 IU, OR, 0.055; 95% CI, 0.008–0.386; P = 0.03).

COVID-19 mortality is still significant in spite of aggressive multitarget therapy and cardiac complications are not infrequent.[7] Advanced age, male sex, and diabetes were associated with unfavorable outcome, as already established by much larger series.[7] The main finding was that therapeutic anticoagulation was associated with a reduced risk of death. This finding can only be considered as hypothesis-generating, due to many possible confounders and unbalanced matching of the 2 groups on or off therapy. Treatment involving oral anticoagulants already used prior to admission which remained unchanged during infection may have favorably affected outcomes by attenuating the damaging effect of the virus' first strike on the endothelium and the coagulation system.[8] Therapeutic doses of heparin were also protective, possibly also due to an antiviral and endothelium-protective effect achievable through higher concentrations of this versatile drug.[9] Although the small sample size and inherent bias of an observational study require caution, these data are coherent with increasing evidence suggesting that since COVID-19 infection is associated with increased blood coagulation, anticoagulation treatment may show benefits which outweigh the risks of bleeding.[10] Obviously, any small, retrospective, observational report without a control group has the scope for sharing of experiences while there is no surrogate for simple, large, multicenter trials based on randomization, which represents the only possible way to avoid mistakes fueled by overenthusiastic expectations.[11]

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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