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Polypharmacy Management in a Gender Perspective: at the Heart of The Problem. Analysis of Major Cardiac Diseases, Sars-Cov-2 Affection and Gender in a Cohort of Patients in Internal Medicine Ward

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Abstract: Background: Covid-19 patients with any pre-existing cardio-vascular disease (CVD) are at highest risk for viral infection and for developing of severe disease. Pathophysiological mechanism is characterized by the viral link to Angiotensin-Converting Enzyme 2 (ACE2) and the involvement of the endothelial system with the release of cytokines and direct damage on myocardium, micro thrombosis, and alterations of oxygen diffusion. Aim of the study is to analyze clinical course, treatment and outcome in patients (gender stratified) with pre-existing CVD. Methods: Out of the 1299 (700 M/599 F) patients admitted to Internal Medicine COVID Unit of "Castelli Hospital", Lazio, Italy, from 01/01/2021 to 31/12/2021, 278 patients (167 M/111 F), mean age 76 (76 M/75 F) had previous CVD. Demographic characteristics, length of the stay (LOS) and oxygen therapy were evaluated. Results: Most common CVD pathologies were Hearth Failure (HF): 131 (72 M/59 F), Atrial Fibrillation (AF): 45 (25 M/20 F), Myocardial Infarction (MI): 26 (19 M/7 F) and associations among them. 100% of CVD COVID patients underwent Non-Invasive Ventilation (NIV) and were treated with more than 5 drugs. HF was linked with increased LOS (23 days) compared to AF (21 days), MI (18 days) and no CVD (16 days). Overall mean LOS was 16,5 days. 21,4% of total patients had CVD. Conclusions: Timely identification and evaluation of patients with pre-existing CVD are fundamental for adequate treatment based on gender, severity and state of illness and for risk reduction.

Keywords: polypharmacy; gender medicine; COVID 19; Sars CoV 2; cardiovascular disease

1. Introduction

Since December 2019, Sars-Cov-2 has been spreading around the world from Wuhan, Hubei Province, China. In 2020, WHO declares COVID-19 (Sars-CoV-2-related disease) as a pandemic. (1)(2)(3) (4)

COVID-19 disease can occur in different clinical forms; full-blown forms can cause pneumonia, respiratory failure and in severe cases Acute Respiratory Distress Syndrome (ARDS). Patients with comorbidities and all using a large number of medications are the most vulnerable, especially those with pre-existing cardiovascular disease (CVD) (5) (6) (7) (8).

Other clinical forms may affect the nervous system (9), mental health (10) or persist beyond the end of the acute infection, these are referred as "Long COVID" syndromes (11) (12) (13), another condition that leads to the use of complex therapies. However, in addition to respiratory symptoms, Sars-CoV-2 can trigger a overproduction of proinflammatory cytokine and chemokines storm (tumor necrosis factor- α , interleukin (IL) 1 β and IL-6), resulting in multiorgan damage(14)

Underlying CVD is a common condition among hospitalized patients with COVID-19 and is associated with a higher risk of serious illness and mortality. Cardiovascular involvement is often present in critical cases and patients with pre-existing CVD or underlying heart failure appear to be susceptible to myocardial lesions (15) (16). Therefore, it is of fundamental importance to understand the mechanisms that underlie cardiovascular damage from COVID-19.

Several studies have shown that the interaction between the viral spike (S) protein and angiotensin-converting enzyme (ACE) 2, which triggers entry of the virus into host cells, is likely to be involved in the cardiovascular manifestations of COVID-19(17)

The damage after Sars-COV-2 infection may occur at different stages of the disease, and for each stage different physio-pathological mechanisms are involved. Cytotoxic damage is associated with virus infiltration into cells expressing ACE 2 receptors (pneumocytes, endothelial cells, cardiomyocytes, neuronal cells) causing acute lesions in lungs, vascular system, myocardium and brain; it usually happens at the early stages of the disease (18) (19).

Literature shows the renin-angiotensin-aldosterone system (RAAS) role in the patients, in which Sars-CoV-2 uses ACE2 for binding to the surface of epithelial cells. However, data on the effect of RAAS inhibitors in COVID-19 patients are not unique. Heart, lungs, kidney and gastrointestinal tract have the higher expression of ACE2 and it justifies systemic and pulmonary hypertension, heart failure, myocardial infarction, and diabetic cardiovascular complications induced by abnormal ACE 2 activity. Potential therapeutic strategies may include preventing the binding of human ACE2 and Sars-CoV-2. (20)

As the disease progresses, damage worsens, as a result from hypoxemia, local inflammation and micro thrombosis. Also the increase in cytokines circulation has been demonstrated to be the cause of damage in multiple organs (e.g., stress cardiomyopathy, myocarditis, vasculitis-like syndromes), and systemic inflammation, or catecholamine rush, associated with plaque rupture or blood's hypercoagulability (thrombotic damage ischemia) (15) (21) (22).

Subjects with CVD are generally adults, elderly and with several comorbidities; moreover age-related immunological quiescence is likely to be associated to severe infection, and is considered a predisposing factor (4) (23) (24). (25) (26)

Since the beginning of the pandemic, it has been clear that the presence of CVD represents a risk factor that increases the case fatality rate more than any other comorbidity. In a report involving 1591 patients with COVID-19 who were admitted to the Intensive Care Units (ICU) in Italy, 49% of patients had pre-existing hypertension, 21% had CVD and 17% had diabetes (27). Furthermore, in a report of 393 consecutive patients hospitalized with COVID -19 in New York, USA, up to 50% of patients had hypertension (54% of ventilated patients), 36% had obesity (43% of ventilated patients), 25% of patients had diabetes (28% of ventilated patients) and 14% of patients had coronary artery disease (19% of ventilated patients) (28).

On the other hand, both CVD and COVID-19 have a different impact on men and women (29) (8).

ASL Roma 6 is a typical Italian Local Healthcare Facility (Azienda Sanitaria Locale, ASL) which is the administrative, commissioning and service provision center for all operations related to Public Healthcare in Italy under the National Healthcare Service. ASL Rome 6 is representative for both population and complexity (by orogeographical characteristic and Hospital-Territorial integration policies) (30). "Ospedale dei Castelli" is the

only COVID Hospital in the entire ASL that hospitalized every COVID patients from all ASL Emergency Rooms.

Since November 2021, Italy has equipped itself with a network of nineteen selected "sentinel hospitals" that periodically send their reports to the Ministry of Health for realtime monitoring of the ongoing COVID epidemic. The network is coordinated by the Italian Federation of Healthcare and Hospitals (FIASO, Federazione Italiana Aziende Sanitarie ed Ospedaliere) and ASL Roma 6 was the only representative healthcare facility in Lazio. Units of the "Ospedale dei Castelli" COVID-19 Medicine wards are also equipped with wireless monitoring systems of vital parameters and electrocardiographic traces. These devices are particularly useful in patients with cardiovascular diseases as they allow early identification of cardiovascular events such as arrhythmias, ischemic alterations and sudden deaths with a 2:1 rate compared to the unmonitored patient. Identification of the Monitoring Tool and Procedure. The WIN@Hospital system (WINMEDICAL, Navacchio, (PI), Italy) is a portable wireless system (Medical Class IIA) that allows continuous, real-time vital signs monitoring, automatic calculation of the NEWS (National Early Warning Score) [16] score, and the creation of a personalized alert system for every single patient through a portable device (tablet or phone), without the necessity of a constant presence of nursing staff. Monitored vital signs are cardiac rate (expressed in beats per minute or BPM or beats/minute), respiratory rate (in acts/minute), blood pressure (in mmHg, millimeters of mercury), peripheral saturation (percentage of oxygen-binding hemoglobin), temperature (in Celsius grade), and position of the patient (orthostatism/clinostats). The WIN@Hospital system is assembled by one module for every parameter, core unit, battery, and wireless connection unit. Overall, the dimensions are $2.5 \times 2 \times 10$ cm (thickness \times height \times width), and the weight is 0.2 kg. By web app, it is possible to customize alerts for every parameter and for every patient before and during monitoring. A preview pilot study was conducted in 2019 in the internal medicine ward of Ospedale dei Castelli (ASL Roma 6, Lazio) and the territorial department of ASL Roma 6. A web app was provided to randomize the patients (clinician does not know randomization criteria) based on their age, sex, weight, and pathologies. (32) (33) (34).

The COVID medical department is organized in such a way to accommodate patients with different intensity of care and different complexity. The number of beds vary according to epidemiological needs so that the department is classified as a "projection department". (4) (31)

The multiple COVID waves have forced the Hospital to configure a dynamic model of organization of the several areas of hospitalization in response to the clinical characteristics of the patients. The model was developed in terms of intensity, complexity and comorbidity offering operators the opportunity to develop specific skills to manage patients in need of semi-intensive care in the area of medical hospitalization. The "wave" trends also forced healthcare facilities to often reallocate staff and beds attributable to other specialties for NO-COVID patients. This model requires the need for constant staff training in the wave growth phase followed by a plateau phase and a subsequent "retrocession" phase after the reallocation of personnel in structures with less intensity-care or organizational complexity.(18) In addition, COVID-19 emergency should give rise to a new form of assistance: the creation of a dynamic "Multidisciplinary high-complexity Team" able to support the Departments of Internal Medicine in managing high-complexity patients, whose availability depends on the pandemic progression. The clinical pharmacist is a member of this interdisciplinary team in the hospital setting and is fundamental in administering early treatments for COVID-19 (i.e. monoclonal antibodies) and complex treatment for patients with COVID and cardiovascular diseases.

2. Aim of the study

Aim of the study is to analyze clinical course, treatment and outcome in patients (gender stratified) with pre-existing CVD that were admitted at the "Ospedale dei Castelli".

3. Materials and Methods

The study was designed as an observational retrospective analysis of data from clinical documentations of all patients with a complete dataset, admitted to Internal Medicine COVID-19 Units of "Ospedale dei Castelli" from January 1st 2021 to December 31th 2021. It was conducted in order to evaluate patients with previous CVD Heart Failure (HF, an heterogeneous condition in which the heart is unable to pump out sufficient blood to meet the metabolic need of the body), Myocardial Infarction (MI, necrosis of the myocardium caused by an obstruction of the blood supply to the heart), Atrial Fibrillation (AF, abnormal cardiac rhythm that is characterized by rapid, uncoordinated firing of electrical impulses in the upper chambers of the heart) and their combination. Definitions of HF, MI and AF were derived from by National Institute for Health (NIH), National Library of Medicine, MeSH (last access 04/07/2022). Admission in COVID-19 Units was based on positive molecular Sars-CoV-2 test and chest CT with crazy paving/ground glass aspects. Number of patients (total/gender-related and % of total CVD Patient/% of total patients), age (mean and gender-related), spontaneous or Non Invasive Ventilation (NIV) use and Length of stay (LOS) (mean and gender-related) were analyzed.

Definitions of "gender" was derived from by NIH, National Library of Medicine, MeSH (last access 04/07/2022): "gender" is "a person's concept of self as being male and masculine or female and feminine, or ambivalent, based in part on physical characteristics, parental responses, and psychological and social pressures. It is the internal experience of gender role".

Since the analytical perspective taken under consideration is the one of the Hospital, the economic analysis considered Length of Stay (LOS) as the main driver of the cost estimation together with polypharmacy.

Outcome data were compared both to the LOS data and to the intensive care hospitalization data related to recovered and dead patients. The data came from the analytical Instant Report of the COVID-19 organizational model published by the Altems website of the Università Cattolica di Roma (4).

With regards to the day of hospitalization value, the estimation used was the one of the Healthcare Datascience Lab (HD-LAB) from Università Carlo Cattaneo – LIUC di Castellanza in cooperation with Azienda Ospedaliera Nazionale SS. Antonio and Biagio and C. Arrigo, based in Alessandria, and Associazione Ingegneri Gestionali in Sanità. The following cost items have been taken into consideration: human resources involved in the assistance path, devices, equipment and DPI used, lab services, diagnostic services, medicines given to patients, catering and cleaning services.

Ethical review and approval were waived for this study, due to the study being conducted on already available data repository. Permission for data usage granted by Italian Law (General Authorization of the Privacy Authority n°9-Autorizzazione generale al trattamento dei dati personali effettuato per scopi di ricerca scientifica, 15 December 2016) and EU Law (EU Regulation n. 119/1, 4 May 2016).

Statistical analysis was performed using Microsoft Excel v.2016 and Stata v.17.0.

Whelch t test (also known as Student's t test for unequal variances) for independent samples was used for mean comparison in LOS between male and female patients.

Barber-Johnson nomogram was also used in order to show differences in LOS, turnover index and bed occupation rate among cohorts.

4. Results

4.1. CVD COVID patients

Total COVID patients with CVD: 278 (167 M/111 F). They were 21,4% of total COVID patients, whose grand total was 1299 (700 M/599 F).

Most common CVD in COVID patients was HF (131 patients), followed by association MI+HF (57), AF (45), MI (26), HF+MI+AF (19), AF+MI (5) and HF+AF (5).

Overall Mean LOS was 16,5 days (17 M/16 F); however, LOS was not evenly distributed across all subgroups (Figure 4, Table 3), with men showing a longer LOS in all groups but one (HF+AF).

152 (11,71%) patients died (102 M/50 F); they all had at least one CVD.

100% of CVD COVID patients (167 M/111 F) underwent NIV and were treated with more than 5 drugs.

Results of archive data analysis are shown in Figures 1-5 and in Tables 1-2. Subgroup analysis is also reported narratively.

PATHOLOGY	CHARACTERISTICS	OVERALL	MALE	FEMALE
MYOCARDIAL INFARCTION (MI)	Number of patients	26(100%)	19(73%)	7 (17%)
	% of CVD COVID patients	9,36	11,4	6,3
	% of total patient	2	2,72	1,17
	Age	75	73	82
	LOS	18	19	16
ATRIAL FIBRIL- LATION (AF)	Number of patients	45(100%)	25 (55%)	20(45%)
	% of CVD COVID patients	16,1	15	18
	% of total patient	3,44	3,57	3,34
	Age	75	75	76
	LOS	21	22	20
HEART FAILURE (HF)	Number of patients	131(100%)	72(55%)	59(45%)
	% of CVD COVID patients	47,16	43,2	53,1
	% of total patient	10,1	10,3	9,8
	Age	78	75	82
	LOS	23	25	19
HA+HF	Number of patients	57(100%)	39(68%)	18(12%)
	% of CVD COVID patients	20,5	23,4	16,2
	% of total patient	4,4	5,58	3
	Age	80	79	82
	LOS	16	16	15
HA+AF	Number of patients	5	3	2
	% of CVD COVID patients	1,8	1,8	1,8
	% of total patient	0.38	0,43	0,33
	Age	72	73	72
	LOS	12	17	8
AF+HF	Number of patients	5(100%)	3(60%)	2(40%)
	% of CVD COVID patients	1,8	1,8	1,8
	% of total patient	0.38	0,43	0,33
	Age	72	73	72
	LOS	12	17	8
HA+HF+AF	Number of patients	19(100%)	16(84%)	3(16%)
	% of CVD COVID patients	6	9,6	2,7
	% of total patient	1,52	2,29	0,5
	Age	79	78	84
	LOS	12	13	11

Table 1. Patient's charatheristics.

CVD: cardiovascular disease; LOS: Length of stay.

DISEASE	MALE (%)	FEMALE (%)	TOTAL (%)
MYOCARDIAL INFARCTION (MI)	4 (80)	1 (20)	5 (100)
ATRIAL FIBRILLATION (AF)	3 (60)	2 (40)	5 (100)
HEART FAILURE (HF)	20 (53)	18 (47)	38 (100)
MI+HF	17 (65)	9 (35)	26 (100)
MI+AF	0	0	0
AF+HF	10 (71)	4 (29)	14 (100)
MI+HF+AF	7 (87,5)	1 (12,5)	8 (100)
TOT CVD	61 (63,5)	35 (36,5)	96 (100)
TOT NO CVD	44 (41,5)	62 (58,5)	106 (100)
ТОТ	110 (54,5)	97 (45,5)	202 (100)

Table 2. Deaths.

CVD: cardiovascular disease;.

Table 3. Mean Length of Stay (days).

DISEASE	MALE	FEMALE	TOTAL
MYOCARDIAL INFARCTION (MI)	26	20	23
ATRIAL FIBRILLATION (AF)	18	15	17
HEART FAILURE (HF)	22	20	21
MI+HF	16	15	16
MI+AF	24	30	27
AF+HF	17	8	12
MI+HF+AF	12	11	12
TOT CVD	19	17	18
TOT NO CVD	19	17	18
ТОТ	19	17	18

CVD: cardiovascular disease; LOS: Length of stay.



Figure 1. Relationship between total patients and CVD ones.



Patients' Gender

Figure 2. Number of CVD patients, stratified by gender.



CVD vs No-CVD patients

Figure 3. CVD and no-CVD patients, stratified by gender.



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Figure 4. Mean age in CVD and no-CVD patients.

Myocardial Infarction (MI)

Myocardial Infarction represent the last common CVD with 26 patients (19M/7F). They represent 9,36% of CVD COVID patients (2% of total). Mean age was 75 (73M/82F) and mean LOS was 18 days (19M/16F).

Heart Failure (HF)

Heart Failure represent the most common CVD with 131 patients (72M/59F). They represent 47,16% of CVD COVID patients (10,1% of total). Mean age was 78 (75 M/82 F) and mean LOS 23,5 days (25M/19F).

Atrial Fibrillation (AF)

Atrial Fibrillation is the second most common CVD with 45 patients (25M/20F). they represent 13,8% of CVD COVID patients (3,44% of total). mean age was 75 (75M/76F) and mean LOS 21 days (22M/20F).

MI+AF

5 patients presented a combination between HA and AF (3M/2F), they represent 5,3% of CVD COVID patients (0,38% of total). Mean age was 72,5 (73M/72F) and mean LOS 12,5 days (17M/8F).

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MI+HF

Myocardial Infarction+Heart Failure is the most common combination of CVD with 57 patients (39M/18F). They represent 20,5% of CVD COVID patients, (4,4% of the total). Mean age was 80 (79M/82F), mean LOS 15,5 days (16 M/15F)

MI+HF+AF

19 patients presented the triple association (16M/3F). They represent 6% of CVD COVID patients (1,52% of total). Mean age was 79 (78M/84F), mean LOS 12 days (12M/F).

Using WIN@Hospital system for patients' monitoring, nurses saved a minimum of 49,6 minutes to a maximum of 58,1 minutes/day on time spent monitoring each patient. A trend towards reduction of major complications in the monitored patients compared to not monitored patients appears to be seen 31% versus 45%. Decrease in mortality (7.3% versus 23.9%) has been observed. Arrhythmias, acute coronary syndrome and respiratory failure detection doubled in non-monitored patients.

5. Discussion

CVDs, in COVID-19 patients, are only common in patients over 70. On average, among COVID-19 patients, LOS of men is one day longer than that of women. Such a difference does not exist among COVID-19 patients who are not affected by CVD. In COVID-19 patients the difference by gender is not significant while it is in patients affected by persistent CVD: men are 52% of the non-CVD COVID-19 patients while they are 60% of the CVD COVID-19 patients.

There are no significant differences on drug therapy and the number of drugs used which always appear more than 5 in both male and female patients affected by COVID and CVD.

Visual comparison of LOS between COVID IM wards and non-COVID IM wards, through Barber-Johnson nomogram, both synchronic and diachronic, shows that the LOS in the non-COVID-19 wards is less than a half of that of the COVID wards (4): that means that COVID-19, being itself a slow resolution pathology, has an impact on LOS. In the COVID-19 + CVD group, difference in gender has also a significant impact, furtherly increasing LOS and also slowing recovery from the primary disease.

LOS for COVID patients with combinations of CVD has been reported to be shorter than no-CVD patients, and this apparent LOS paradox can be easily explained: LOS is shorter for CVD COVID patients because combinations of CVD are an important negative prognostic factors, and death occurs earlier in such patients, whereas no-CVD patients show a higher rate of recovery: CVD patients simply "fail faster" more often than not.

Higher resources uptake is observed to be directly associated with the increase of the complexity of care, which means an increase in the length of stay in the Unit where the patient is hospitalized, increase of pharmaceutical cost and also an increase in the reimbursement tariffs that are expected to be associated to single DRGs and therefore an increase in the overall public healthcare expenditure. This information can certainly represent a fundamental element that can lay the foundations, from a policy making and health planning profile, for a comparison between hospital practices and reference rates for the health activities carried out.

Moreover, the increase in the resources uptake raises important concerns with particular regard to the opportunity costs. It is generally known that in a context of limited resources leading to budget constraints, issues related to the effect allocation of resources should be considered as a key driver to pursue productivity gains. In this specific case, the design and the implementation of specific care pathways, could lead to the achievement of scale and scope economies thus also leading to an increase in the quality of care.

It is also important to consider that the appropriate, effective safe and efficient design of care pathways should take into account the correct definition of tasks and responsabilitites given to different health professionals. In this case, when possible and consistent with the international guidelines and the Italian laws, task redefinition should be pursued also shifting some responsabilities from MDs to specialized nurses. Appropriate training is of course requested.

In particular, several elements have been outlied, such as overall resources usage, the process critical factors and average LOS, based on the clinical condition of the patient and on the seriousness of the pathology which also implicated a low intensity cure assistance (characterized by the use of beds in the traditional medical areas without equipment for patients in need of non-invasive ventilation), average complexity (in which all emplacements are designed to manage sub-intensive therapy patients with non-intensive ventilation), and the high cure intensity and aid.

According with literature (35) (36), the total costs of hospitalization in Medium Intensity areas such as Covid Medicine is €9157/day/patient, against €22,210.47/day/patient in High Intensity setting such as ICU or Intensive Therapy wards. Management of High intensity CVD COVID patients in Covid Medicine wards with NIV devices generate a net saving of €13,053.47/day/patient. Just considering the sample of the 278 CVD COVID patients hospitalized in "Ospedale dei Castelli" Hospital, the savings would amount to €3.628.864,66. An undisputed economic advantage is generated from managing CVD COVID-19 patients in a COVID-19 Medicine unit, if it is structured with sub-intensive criteria (NIV and continuous vital signs monitoring), and transferring to Intensive Care Unit only those patients who require invasive ventilation. Patients managed appropriately in a medium-intensity care setting such as a COVID-19 Medicine ward would allow to save over € 13,000/day/patient.

Future studies could investigate more accurately potential savings also with use of parametric methods and a quasi – experimental approach.

Presence of one or more CVD increases LOS and subsequently inflates costs (every hospitalization day costs \in 582,38 in medium-intensity care units and \notin 1278,50 in high-intensity ones) (37) (38) (39) (40) (35). On average, male COVID patients stay at least one day more than female patients and, consequently, they are more expensive than female. (29) Also, it must be pointed out that increase in LOS has also impact on the outcome, since increased length of stay is an independent predictor for complications, morbidity and negative outcomes in general. Moreover, they are at higher risk of being overloaded with drugs, especially antibiotics, the use of which in Italy has sometimes been subject to misconceptions from both clinicians and patients alike. (41)

Throughout this historical period, in order to better manage the pandemic, the evolution and, above all, the clinical course of the disease, assistance structures necessarily had to restructure their processes of diagnosis and treatment, the spaces as a whole, the supply chains and the related deviations, with a consequent substantial involvement in hospital organization, which has by necessity translated into an economic investment, intended for the treatment, management and treatment of respiratory viral infection from COVID 19. The organizational adjustments put in place to cope with such a high demand were certainly enormous and, focusing attention on the investments made by the hospital to address the health problem, the supporting technologies are those normally used in case of epidemic, pneumonia with evolution in severe respiratory failure and subsequent assisted pulmonary ventilation, in addition to the prevention of complications such as the use of enteral or parenteral nutrition, in cases where the patient is no longer able to feed himself independently, the adoption of these solutions represents an important upgrade in the management of the patient hospitalized in the Medical Area. The new organizational models developed and in particular the management of highly complex patients with the need for non-invasive ventilation in Covid Medicine have demonstrated the effectiveness of management in a "high intensity" medical context, often avoiding transfer to the Intensive Therapy Units with a significant reduction in costs. This model therefore appears promising and can also be applied to pathologies other than Covid such as acute respiratory failure, acute heart failure and persistent arthritis, stroke, severe septic state that can find an appropriate location in areas defined as "high complexity" thus also bringing innovation and development within the departments of Internal Medicine.

6. Conclusions

The prevalence of hypertension and CVD is clinically relevant in patients with COVID-19, particularly in the elderly, and just as it happened with other diseases of the past, long-term consequences may be subject to far future analyses (20) (42). However, in the short term, timely identification and evaluation of patients with pre-existing CVD is fundamental for adequate treatment based on the severity and state of illness and for risk reduction.

In accord with current literature, (12) this study shows that there is a strong relation between gender and COVID outcome in patients with pre-existing CVD, especially if elderly: during the first three COVID waves, the typical patient in the COVID Unit was old and with 3 or more comorbidities, treated with more than 5 drugs. CVD were the most common co-morbidities for such patients. Is already known that CVD risk factors are gender related (46) and this study further shows that their presence impacts on LOS and outcome of patients. (47) HF and AF increase LOS, since they are correlated with the need for more intensive care, such as NIV and the continuous monitoring of vital parameters.

In addition, a prompt identification of such high-risk patients would allow a timely treatment and the reduction of even serious complications, with efficacy also on LOS. Therefore, even a multidisciplinary management of comorbidities, including the participation of the clinical pharmacist, can be an advantage for a correct treatment of patients with CVD and COVID-19 diseases. It is an index of appropriateness and effectiveness of the health promotion and care offered, even if prevention and lifestyle-rules keep playing an important role. Telemedicine also could perform an important role, enabling physicians to ensure a more appropriate management of complex patients, reducing the time to diagnosis, improving efficiency and efficacy of disease management and reducing unnecessary clinic visits and hospital admissions. The miniaturized technologies can improve patient adherence. The detection, characterization and monitoring of major complication, also, reduce cost of hospitalization and mortality and assure better quality of life. The use of wireless monitoring systems allows many of these patients to be safely sent home and to effectively integrate Hospital and Community services. All this can be integrated with targeted pharmacological strategies, especially in the light of recent findings that show how pre-expository prophylaxis and early pharmacological treatment with targeted therapies (such as, antiviral and monoclonal antibodies tailored on the prevalence of a particular serological COVID variant) are effective strategies in reducing the burden of the disease on both the individual and the Health Systems as a whole. (48), (49)

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Conflicts of Interest: The authors declare no conflict of interest. Ethics committee approval was not required because this study was a secondary data analysis of routinely collected data.

Data Availability Statement: Raw data were generated at PO Castelli Hospital. Derived data supporting the findings of this study are available from the corresponding author F.R. on request.

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