EFFECTIVENESS OF A ON-SITE MEDICALIZATION PROGRAM FOR NURSING HOMES WITH COVID-19 OUTBREAKS

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ABSTRACT

BACKGROUND: Nursing homes are highly vulnerable to the occurrence of COVID-19 outbreaks, which result in high lethality rates. Most of them are not prepared to SARS-CoV-2 pandemic.

METHODS: A coordinated on-site medicalization program (MP) in response to a sizeable COVID-19 outbreak in four nursing homes was organized, with the objectives of improving survival, offering humanistic palliative care to residents in their natural environment, and reducing hospital referrals. Ten key processes and interventions were established (provision of informatics infrastructure, medical equipment, and human resources, universal testing, separation of 'clean' and 'contaminated' areas, epidemiological surveys, and unified protocols stratifying for active or palliative care approach, among others). Main outcomes were a composite endpoint of survival or optimal palliative care (SOPC), survival, and referral to hospital.

RESULTS: 272 out of 457 (59.5%) residents and 85 out of 320 (26.5%) staff members were affected. The SOPC, survival, and referrals to hospital, occurred in 77%, 72.5%, and 29% of patients diagnosed before MP start, with respect to 97%, 83.7% and 17% of those diagnosed during the program, respectively. The SOPC was independently associated to MP (OR=15 [3-81]); and survival in patients stratified to active approach, to the use of any antiviral treatment (OR=28 [5-160]). All outbreaks were controlled in 39 [37-42] days.

CONCLUSIONS: A coordinated on-site medicalization program of nursing homes with COVID-19 outbreaks achieved a higher survival or optimal palliative care rate, and a reduction in referrals to hospital, thus ensuring rigorous but also humanistic and gentle care to residents.

KEYWORDS: COVID-19, SARS-CoV-2, community-based long-term care, frailty, multimorbidities

INTRODUCTION

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is beating most countries. Europe, and particularly Spain are one of the most affected areas with accumulated cases and a mortality rates of 504.6 and 61.5 per 100.000 population, respectively in the latter (1, 2). The disease affects more frequently and more severely aged people; as a matter of fact they make up around 30% of all cases, 45-50% of all hospitalizations, and 80% of all deaths (2-4). In these age strata SARS-CoV-2 disease (COVID-19) lethality rate can reach up to 20-40% (3, 4). There are various reasons to explain an increased mortality rate in this age group. There are already known risk factors (immunosenescence, frailty, infection acting as a trigger to decompensate other chronic conditions, and development of geriatric syndromes' cascade) (5); but in the actual pandemic context, there are other evident or subtle reasons, like health-care systems collapse, lack of material and human resources, and disaster situations involving ethical issues, which are contributing to this poor results (6-10).

Additionally, one of the most critical and helpless environments for the expansion of SARS-CoV-2 are nursing homes (11). In these facilities, the impact of COVID-19 on human health by affecting the most vulnerable population, and therefore conditioning the subsequent health-care system saturation, is a real danger that can be devastating (11,12). Data are scarce, but affected nursing home populations may be a significant proportion of all COVID-19 cases in some countries (11-13). Another consequence of this fact is the potential transmission to community, and hence, the persistence of SARS-CoV-2 circulation. As a matter of fact nursing homes are integrated in the community, and their facilities are opened to residents' families, friends and different community resources. Unfortunately, most of them lack structure and work-flows to face an epidemic of this magnitude; many of them are poorly connected with the health-care system, count with lower staff ratio (adjusted to attend

'stable' residents); and have suboptimal staff training and expertise in managing patients with COVID-19 (11-13). Therefore, many COVID-19 outbreaks affecting nursing home residents, staff members and residents' families have occurred (14-16).

In the present work we detail an innovative coordinated on-site medicalization program (MP), which was carried out in response to a sizeable COVID-19 outbreak declared in last days of March 2020, in four nursing homes of Seville province (Southern Spain, 1.942.389 inhabitants, 688.592 of them living in the city) with the aim of offering medically rigorous but also humanistic care to residents with COVID-19 in their natural environment, avoiding the community widespread of SARS-CoV-2 thorough specific and forthright measures, and minimizing hospital saturation, helping therefore to achieve a better and proper use of these resources. Specifically we will describe all details of the MP and its achievements in terms of survival or optimal palliation of treated residents, as well as hospital referral reductions.

PATIENTS AND METHODS

On March 17th, 2020 a 98 year-old patient coming from a nursing home was admitted to Hospital Universitario Virgen del Rocío (tertiary teaching center of Seville with a reference population of 557.576 citizens), and diagnosed with COVID-19. The following days up to 27 new cases coming from this and other 3 similar facilities located in the city of Seville, within the hospital's reference area, were also transferred and diagnosed with the disease. Under these circumstances a Primary Care and Hospital coordinated MP was quickly built. This program contained informatics, medical equipment and material, pharmacy, and human resources to fully attend the outbreaks in the 4 nursing homes on-site. The MP was initiated among 1st and 6th of April, 2020 in all these residential centers.

Reference population and inclusion criteria: The total population was 777 people, 457 of them were residents (86 years-old [Quartile1-Quartile3 (Q1-Q3)=79-91], 75% women), and

320 were staff-members. A description of the magnitude of the outbreak is detailed in Table 1. All residents diagnosed with COVID-19 were included in the MP. All staff-members were treated and followed-up with the hospital current management protocols, but were excluded from the present study.

MP characterization: The program contained the following critical processes and interventions carried out on-site in all 4 nursing homes:

1. Locating a 'clean room' for informatics equipment, clinical work, consulting and writing in electronic clinical charts, and administrative tasks. Full connection with health-care electronic information systems.

2. Locating a secure locker room for health care workers' dressing and undressing. Ensuring personal protective equipment supplies to all MP team members.

3. Universal SARS-CoV-2 testing to residents and staff members. Real-time polymerase chain reaction (RT-PCR) for the detection of specific viral ribonucleic acid (RNA) from nasopharyngeal swab-smears, and lateral flow serologic method from fingerstick blood samples for the detection of specific antibodies against SARS-CoV-2 were performed. For these purposes the Allplex® 2019-nCoV RT-PCR assay (Seegene Inc., Seoul, South Corea), for detection of gene targets ORF1ab and N; the VIASURE® SARS-CoV-2 RT-PCR assay (CerTest Biotec S.L., Zaragoza, Spain), for detection of gene targets RdRP, E and N; and the Wondfo® SARS-CoV-2 Antibody Test Lateral Flow Method assay (Guangzhou Wondfo Biotech Co Ltd, Guangzhou, China) for the detection of IgM and IgG antibodies, were implemented. We performed both methods at once in order to accelerate decision making and to avoid acute infection confirmations delay.

SARS-CoV-2 acute infection was defined either as the detection of viral ribonucleic acid by RT-PCR ('positive nasopharyngeal swab PCR'), as the presence of IgM or IgM and IgG antibodies ('positive serology'), or both.

4. Establishment of a 'clean area' with rooms and common spaces to which uninfected residents were moved, and a 'contaminated area' with rooms and common spaces to which residents with confirmed infection were moved. Warrant the compulsory use of personal protective equipment to all members of the work team while remaining in the contaminated area.

5. Specific training of staff members in the management and care of COVID-19 patients. Separation of those working in the clean area and those working in the contaminated area, with prohibition to change shifts between professionals from these two areas. Proper clinical attention and quarantine of staff members with confirmed SARS-CoV-2 acute infection until obtaining a negative nasopharyngeal swab PCR (they were tested weekly, counting from the first day without symptoms).

6. Meticulous epidemiological survey and follow-up to trace the outbreaks' origin and evolution.

7. Electronic admission of all residents with demonstrated SARS-CoV-2 infection, which allowed electronic health records' checking, writing, ordering blood extractions, and drug prescribing as if patients were in-hospital.

8. Enough provision of equipments, expendables and drugs: material for blood extractions, intravenous and subcutaneous lines, intravenous fluids, oxygen therapy, electrocardiographs, a portable ultrasound, and hospital medications (antiviral agents, intravenous drugs...) among others.

9. Provision of health-care workers (physicians and nurses), covering clinical attention 24 hours during 7 days in the week. They were mixed teams with Primary Care (Family and Community Medicine), Hospital (Internal Medicine), and Emergency (Emergency Medicine) professionals. A reckon of 60 health-care workers were mobilized (35 physicians and 25 nurses).

10. Elaboration of a common clinical management and treatment algorithm, and a common communication protocol to daily inform families by phone about the clinical status of both, affected and not affected residents.

Clinical algorithm and treatment protocols: The main clinical algorithm is detailed in Figure 1. After a thorough clinical evaluation, based on the 6-month adapted 'surprise question' ('would I be surprised if this patient dies in the next six months?'), patients' and families' preferences, and after consulting patient's advance directives for life-support, all residents with COVID-19 were offered either active standard care or advanced palliative care.

All patients were daily assessed for early mobilization, sitting and starting physical therapy. Clinical cure was defined after three days of being asymptomatic, and microbiological cure when the patient tested a control negative nasopharyngeal swab PCR after clinical cure. All patients were isolated in the 'contaminated area' for 14 days after being asymptomatic; then, were performed a control nasopharyngeal swab PCR before discharging and transferring them to the 'clean area'.

Active standard care: Patients in this group were actively treated with hydroxycloroquine (HCQ) with or without lopinavir/ritonavir (LPV/RTV) (under judgement of clinician in charge) with the addition of adjuvant and antimicrobial treatments in the circumstances detailed in Supplementary Appendix, Table S1. Daily measurement of vital signs, clinical follow-up until 3 days after being asymptomatic, and at least during the whole antiviral treatment were carried out. Blood sample extraction to assess biological parameters was available. Point of care ultrasonography (POCUS) (Vscan Extend Dual Probe®, GE Healthcare, Little Chalfont, UK) was performed if oxygen saturation fell below 94% or 5 or more points from patient's baseline saturation. Any clinical, biological, or ultrasound data of macrophage activation syndrome-like disease were monitored to implement first-line anti-inflammatory treatment.

Advanced palliative care: All patients in this group were offered a single room, ensuring comfort, personalized care, and spiritual support. A global multidimensional evaluation was performed with symptomatic focus and medications were daily adjusted. Oxygen therapy and antimicrobials were used when dyspnea/hypoxemia or bacterial co-infection were present, respectively. In some patients corticosteroids were also used, but never before the 5th day of symptoms beginning. Clinicians were proactively aware of end-of-life/agony symptoms and signs occurrence; in this situation, palliative sedation as well as the accompaniment of one family member were offered; the accompanying family member was offered a personal protective equipment with specific instructions on its use. An optimal palliative care was defined when the complete process (offering, acceptance, and materialization of all the above mentioned issues, including the offering of palliative sedation and accompaniment if indicated) was accomplished.

Treatment protocols included antiviral treatment, adjuvant treatments, and antimicrobials are detailed in Supplementary Appendix, Table S1.

Follow-up, referrals and discharge: All patients were followed-up according to the previously detailed clinical algorithm. For the purposes of this study a 30-day period after SARS-CoV-2 infection confirmation was established. When clinically indicated (Figure 1), referrals to hospital were organized and programmed with the clinicians attending in-hospital COVID-19 patients. Patients who met previously detailed clinical and microbiological criteria of cure, were discharged and moved to the clean area.

Demedicalization criteria: After 14 days of the last confirmed COVID-19 case, the nursing home was eligible for demedicalization. In this process the following requirements were ensured: 1. A contingency plan with infection and prevention measures, active surveillance, actions in case of new infections, and provision of spaces and rooms for possible future 'contaminated areas'. 2. Urgent notification of the appearance of suspected cases compatible

with COVID-19. 3. Continuous training to staff members. 4. Staff members control through daily temperature measurement and a responsible declaration at the entrance to the workplace of not having symptoms compatible with COVID-19, and in case of symptoms onset, urgent notification. 4. Public and auditable weekly check-list of the infection control measures.

Data collection and variables: A complete set of demographical, clinical, functional, and pharmacological data were retrospectively collected from all the cohort of included patients. Clinical data included the different diseases, and all possible comorbidities, previous medications, functional parameters by means of Barthel's index, prognostic parameters by means of PROFUND indexes, different symptoms and signs, medical treatments, and outcome (17, 18). These data were collected by clinicians in charge, who were active members of the investigation team.

The main outcome was a composite variable, which was accomplished if survival or an optimal palliative care (SOPC) of residents with COVID-19 occurred. For this purpose, we looked at survival as dichotomous, so subjects were categorized depending on whether they survived COVID-19 or not after the follow-up period. An optimal palliative care was defined as detailed previously.

Secondary outcomes were survival in those patients stratified to active standard care; number of patients who needed to be referred to hospital; and the mean number of hospital referrals per week. For this purpose, we looked at survival as both a dichotomous and as time-dependent outcome. For the dichotomous outcome, subjects were categorized depending on whether or not they survived COVID-19 after the follow-up period. For the continuous outcome, survival time was defined as the number of days between the symptoms onset date (diagnosis date in those patients with asymptomatic infection) and the date of death.

At last, we evaluated the daily number of community-acquired new COVID-19 cases, as well as the total cumulative incidence of citizens living in Seville city during the same time period, in order to empirically establish possible relations between both epidemic curves.

Statistical analysis: The dichotomous variables were described as whole integers and percentages, and the continuous variables as mean and standard deviation (or median and interquartile range in those with no criteria of normal distribution). The distribution of all variables was analyzed with the Kolmorogov-Smirnov test. Possible differences in SOPC, survival, patients needing hospital referral, and hospital referral rates per week were firstly investigated performing the Chi-square test (with the Yates correction and, when necessary, the Fisher exact test), the Student's *t* for normally distributed quantitative variables, and Mann-Whitney U test in the case of quantitative variables that were not normally distributed.

We included the factors which showed statistical differences in unadjusted analysis, in a multivariable backward stepwise logistic regression model in order to obtain those independently associated to SOPC. With respect to survival in patients stratified to receive active standard care we also included the factors which showed statistical differences in unadjusted analysis, in a multivariable Cox proportional hazards model for time to death, in order to obtain those independently associated to survival. In this group of patients we also performed Kaplan-Meier curves (and log-rank test), considering death as a time-dependent variable, to assess differences in survival trajectories of those diagnosed before or during the implementation of the MP.

The strength of associations was quantified by calculating *odds ratio* (OR) using 95% confidence intervals. Statistic analysis was performed by Máximo Bernabeu-Wittel using the SPSS 22.0 software.

Ethical aspects: All patients or their legal representatives accepted the use of their anonymous clinical data for clinical research purposes. The study was approved by the by the local ethics committee (internal code 1199-N-20). In this retrospective project the collection, process and analysis of all data was anonymously carried out, and only for the purposes of the project. All data were protected in accordance with the European Union directive 2016/679 of the European Parliament and the European Council, of April 27, 2016, regarding the protection of persons and their personal data. All authors declared no conflict of interest with respect to this work.

RESULTS:

In total 357 people out of 777 (46%) were infected by SARS-CoV-2; of them 272 out of 457 (59.5%) were residents, and 85 out of 320 (26.5%) staff members (Table 1). The median number of days since first resident was diagnosed with COVID-19 until the start of MP were 12 [11-14], and the median duration of MP was 39 [37-41] days. The main differential clinical and biological features of all residents affected are detailed in Table 2. Briefly, they were mostly aged women, suffering of multiple chronic conditions, with functional decline and polypharmacy. The most frequent symptoms were fatigue and global deterioration, followed by low-grade fever, dyspnea, cough, anorexia, diarrhea and delirium. Sixty-six residents (24%) developed no symptoms, or these were mild. All staff-members developed mild to moderate symptoms or stayed asymptomatic.

Residents affected were diagnosed with a positive nasopharyngeal swab PCR test (229 (84.2%)), rapid serological test (21 (7.7%)), or both (22 (8.1%)). After the initial evaluation 189 (69.5%) were proposed for active standard care and 83 (30.5%) for advanced palliative care. The most frequent interventions, were oxygen therapy (114 patients, 42%), intravenous lines and fluids (86, 32%), parenteral drugs (intravenous or intramuscular; 64, 23.5%), POCUS (50 procedures, 18.4%), and transfusions (2 patients). In those proposed for

active standard care, according to established protocols (Supplementary Appendix, Table S1), antiviral treatment was administered to 139 (73.5%) patients; the most frequent scheme was hydroxycholoroquine (114 patients, 60%) followed by hydroxychloroquine plus lopinavir/ritonavir (18, 10%), and hydroxychloroquine plus azythromycin (7, 5%). Low molecular weight heparin was administered to 119 patients (44%), antimicrobials to 62 (23%), and systemic corticosteroids to 57 (21%).

All patients proposed for advanced palliative care were treated with supportive care. Additionally they were treated with low molecular weight heparin (36, 43%), antimicrobials (33, 39.8%), antiviral drugs (30, 36%), and corticosteroids (21, 25%).

The most frequent complications and main outcomes are detailed in Table 3. A 13% (n=24) and a 45% (n=37) of patients proposed for active standard- or for optimal palliative care died, respectively. In multivariate analysis the main outcome SOPC was independently associated to COVID-19 diagnostic confirmation during MP (OR=15 [3-81], p=.001) among other possible confusing co-variables. In those patients stratified to receive active standard care, survival rates were 82% before MP and 96% during PM (p=.004, OR=3.4 [1.2-10]). In this group, survival time was independently associated to the absence of dyspnea (OR=16 [5-50], p<.001), or fatigue-general deterioration at presentation (OR=5 [1.7-14], p<.001); a lower PROFUND index score (OR=1.17 [1.05-1.3], p=.004); lower serum C-reactive protein (OR=1.009 [1.004-1.015], p=.001), and ferritin levels (OR=1.001 [1-1.001], p=.01); and the use of any antiviral treatment (OR=28 [5-160], p<.001). The differential time-dependent survival in this group of residents diagnosed with COVID-19 before the start or during MP is detailed in Figure 2.

In the epidemiologic survey it was stated, that in all nursing homes, the symptoms onset dates of the first affected staff members preceded in 5.5 (Q1-Q3=2-9.7) days to those symptoms onset dates of the first affected residents (Supplementary Appendix, Figure S1).

The global outbreak dynamics are reflected in Supplementary Appendix, Figure S2. The peak of residents with active infections was reached on April 13th (175 patients), and after this date we observed a progressive fall of these, together with a rise in the number of recovered patients, as well as a stabilization and absence of new cases. The first nursing home fulfilling demedicalization criteria reached them on May 12th, 2020, and the last one on May 14th. Globally, the four outbreaks' median duration was 50 [49-54] days after their start. At the time of writing this article no new cases had been diagnosed since April, 30th 2020, all surviving residents remained without any COVID-19 symptoms. The last microbiologically cured resident was a 99 year-old woman whose control nasopharyngeal swab PCR tested negative on May 21th, 2020. Addressing the same periods of the three preceding years, a noteworthy peak in the number of deceased residents was observed in the four nursing homes, as detailed in Supplementary Appendix, Figure S3.

The peak of new community acquired COVID-19 in Seville city was reached on March 25th, 2020 with 87 new cases. Afterwards, a progressive decline until nowadays residual transmission has occurred (Supplementary appendix Figure S4). Globally, in this first pandemic wave 1094 COVID-19 cases (cumulative incidence 158.8 cases/100.000 inhabitants) have been diagnosed in the city of Seville, 32,4% of them occurred in the nursing home outbreaks, summing up affected residents and staff members living in the city. None of the 60 health care workers taking part in the MP was infected.

DISCUSSION

The incorporation of a coordinated MP in the management and control of four sizeable COVID-19 outbreaks in nursing homes, resulted in significant better outcomes of the composite end point of survival or optimal palliative care, as well as reductions in hospital referral rates. This MP virtuously gathered substantial hospital and primary care resources as well as internal medicine, primary care, and epidemiology professionals during an intense but short time-period.

Specifically the reduction of COVID-19 mortality during MP to nearly 16% was notably lower if compared to other reported outbreaks in long-term care facilities (27-33%) (11, 14, 15); and also when compared to rates of in-patients of our hospital (54% in those over 80 years, data not published) or to patients of same ages in Spain (globally 22%, and 48.5% in those needing hospital care) (2). The MP also achieved as additional benefits, the development of fewer medical complications, and a more comfortable and peaceful care process in those with a previous poor life expectancy.

We think, that the clues to explain benefits of the MP are three: First of all, it enabled an earlier symptoms recognition by well-trained professionals, which led to earlier treatments and support measures; this is an evident fact common to all diseases; in this sense, our data show, that stratifying and treating very old patients with potentially acceptable life expectancy, is safe and of probable benefit; otherwise we could fall in a somehow nihilist deviation of clinical practice (19, 20, 21). Second, it allowed the on-site care in the natural environment of patients, which led to fewer complications, mainly due to less geriatric syndromes occurrence; early mobilization, rehabilitation, and use of common spaces and rooms in the contaminated area for the continuity of activities, prevented the highly frequent complications of hospital care; as a matter of fact rooms of hospital wards dedicated to COVID-19 are isolated, and interactions with patients generally restricted to the strictly

necessary (19). Third, it incorporated humanistic and gentle attention to the most frail and terminally ill residents, enabling a personalized care according to preferences of patients and families; the rush of a pandemic situation should not make palliative care invisible, on the contrary an exquisite stratification and subsequent optimal palliative care has to be offered to this selected population in order to avoid futility and unnecessary iatrogenia (20, 21); in this sense it is important to remark, that optimal palliative care does not mean death; as a matter of fact 55% of patients stratified to optimal palliative care survived COVID-19.

Epidemiological surveys, showed that SARS-CoV-2 could have entered nursing homes either by staff members or by visitors in preceding days to the declaration of national alarm state by the Government of Spain on March 14th, 2020 (22). Then, the virus spread fast, probably because of the same reasons as those already detailed in similar outbreaks (14, 15, 23). The city epidemic curve ran parallel but preceded a few days those observed in the nursing homes outbreaks, which supports the previously commented hypothesis. No impact of the delayed incidental case peak of nursing homes outbreaks was observed in the global epidemic curve of the city; nevertheless we can extract no definitive conclusions because this could reflect the absence of transmission from nursing homes to community due to the MP, the effects of national lockdown measures, or both.

One of the leading results of this study is the complete clinical picture of COVID-19, that we obtained in a large sample of frail elderly people. We observed the typical patterns of COVID-19 less frequently, whereas more subtle and unspecific symptoms and presentations were more prevalent. This has also been observed by other authors and follows the pattern of getting sick in geriatric populations, which is well known with respect to other diseases (24, 25). Of notable remark is the absence of prognostic influence of any comorbidities taken them individually; only their combination in the PROFUND index showed prognostic ability. In contrast, some COVID-19 symptoms and biological parameters like dyspnea, fatigue and

general deterioration, C-reactive protein and ferritin levels, showed a strong independent association with death. The presence of any of these symptoms in old patients with COVID-19, has to put us on alert.

Another remarkable finding was the strong independent association of antiviral treatments with survival. This fact is both concordant as well as contradictory to previous reports and puts in the front line the urgent needs of counting with evidence to optimally treat COVID-19 patients (26-31). In the absence of this evidence, we are of the opinion, that best available choices (those safest drugs with best previous results) should be offered to patients. In this sense we opted to use hydroxychloroquine with or without lopinavir/ritonavir, because of their extensive use in many protocols (29, 30).

The MP was a huge effort on many levels, but the effectiveness shown proved this effort to be worth it. Many voices and societies have emphasized, that nursing homes and other long term care facilities are the most vulnerable environments to the effects of SARS-CoV-2 pandemic (11), urging all actors (community leaders, governments, health and social care authorities) to prioritize them in their strategies (32-34). In some countries like Spain, this fact is even more critical due to its high life expectancy and the significant number of elderly citizens living in these facilities (35). But beyond statements and guidelines, reality also needs pragmatic actions and interventions, because these extraordinary times need our help with unprecedented solutions (36).

The main lessons we have learned after the MP task are also three: First of all we learned, that nursing homes are key elements and one of the main targets in the fight against possible future SARS-CoV-2 pandemic waves; many have considered them in the border of health care and social services, and because of that their connections and boundaries to both systems are somehow imprecise, as many countries have painfully witnessed; it is time to globally rethink the role and place of nursing homes in our societies, and to really work in a

deeper integration of health and social care (11, 23, 33). Second, we learned, that health care resources re-allocation is an effective strategy to manage this pandemic, and that decisive and anticipated actions save lives and prevent unfortunate consequences; one may think, that this mobilization was exaggerated and expensive, but otherwise at least two hundred of these residents would have needed hospital care, so in this scenario the same health care resources would have been used, but in a overcrowded and saturated hospital. And at last we learned, that a true synergistic coordination between Primary and Hospital Care is possible and it works. We all have read a lot about this issue, and know, however, the daily difficulties in its implementation (37). In these extraordinary circumstances integration worked wonderfully, because it emerged from professionalism values: willingness to serve people, altruism, generosity, and mutual respect.

This study has some limitations, that should be remarked. First, the retrospective collection of the cohort's data, which could introduce some biases, as it is already known for this kind of approaches. Second, the confidence intervals for some of the findings are wide, reflecting limits in study power for some analyses. And third, the possible regression to the mean, which is present in most health care initiatives directed towards high-risk populations, could have played a role in the results; however, we think that this effect is not at all present in the obtained data, because when MP started, obviously all patients (included those who were diagnosed previously) were attended; so, these last patients also received the benefits of the program, but were treated in the analysis of end-points as if they had not.

In conclusion our work show, that a coordinated on-site medicalization program of nursing homes with COVID-19 outbreaks achieved better outcomes of survival and optimal palliative care, as well as a reduction in referrals to hospital, thus ensuring rigorous but also humanistic and gentle care to residents.

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Table 1. Global data of the four nursing homes' COVID-19 outbreaks in the city of Seville, Spain.

NURSING HOME	NUMBER OF RESIDENTS	AGE OF RESIDENTS	GENDER FEMALE	DATE OF OUTBREAK START	NUMBER OF AFFECTED RESIDENTS	NUMBER OF AFFECTED STAFF MEMBERS &	NUMBER OF DEATHS IN AFFECTED RESIDENTS
NH1	168	86 [81-92]*	126 (75 %)	March 17th 2020	123 (73%)$	44(35.2%)¶	29 (25%)#
NH2	155	85 [78-89]*	114 (73.5%)	March 23th 2020	93 (60%)$	21 (19.3%)¶	23(24.7%)#
NH3	101	88 [81-92]*	85 (81 %)	March 25th 2020	35 (35.6%)$	11 (17.7%)¶	6(16.7%)#
NH4	33	86 [79-90]*	23 (70 %)	March 26th 2020	21 (63.6%)$	9 (37.7%)¶	3(14.2%)#
TOTAL	457	86 [79-91]*	348 (75 %)	March 17th-26th 2020	272 (59.5%)$	85 (26.5%)¶	61(22.4%)#

NH: nursing home; *Median [Quartile1-Quartile3]; $:with respect to all residents; &:all of them with mild-moderate symptoms or asymptomatic; ¶with respect to all staff members; #:with respect to all affected with COVID19 (lethality)

Table 2. Main clinical features of residents with COVID-19 during four nursing homes outbreaks in Seville, Spain.

CLINICAL FEATURES MEAN (SD)/MEDIAN [Q1-Q3] / Nº(%)	**GLOBAL (N=272)**	**PATIENTS DIAGNOSED WITH COVID-19 BEFORE MP (N=149)**	**PATIENTS DIAGNOSED WITH COVID-19 DURING MP (N=123)**
Age and female gender	87[81-91]; 205 (75.4%)	88 [83-91]; 108 (72.5%)	86 [79-90]; 97 (79%)
Nº of comorbidities per patient	4 [3-6]	4 [3-6]	4 [3-6]
Most frequent comorbidities			
Hypertension	198(73%)	116 (78%)	82 (67%) **(p=.04)**
Dyslipemia	104 (38.2%)	57 (38.3%)	47 (38.2%)
Advanced dementia	103 (37.8%)	55 (37%)	48 (39%)
Osteoarthritis	76 (28%)	42 (28%)	34 (27.6%)
Depression	72 (26.5%)	40 (27%)	32 (26%)
Diabetes mellitus	71 (26%)	40 (27%)	31 (25%)
Mild-moderate dementia	64 (23.5%)	37 (25%)	27 (22%)
NL disease with severe impairment	59 (22%)	25 (17%)	34 (27.6%) **(p=.03)**
Cereborvascular disease	53 (19.5%)	27 (18%)	26 (21%)
Atrial fibrillation	52 (19%)	33 (22%)	19 (15%)
Chronic heart failure	38 (14%)	20 (13%)	18 (15%)
Anxiety disorders	37 (13.6%)	14 (9.4%)	23 (19%) **(p=.03)**
COPD or asthma	36 (13%)	22 (15%)	14 (12%)
Coronary artery disease	34 (12.5%)	29 (19%)	5 (4%) **(p<.001)**
Parkinson disease	30 (11%)	17 (11.4%)	13 (10.6%)
Hypothyroidism	24 (8.8%)	13 (8.7%)	11 (9%)
Basal Barthel´s Index	49.5 (30)	47 (29)	52 (31)
PROFUND index	8.2 (4)	8.5 (4)	7.7 (3.5)
Nº of chronic prescribed drugs / Patients with extreme polypharmacy (>10 drugs)	7.2 (3.6) / 50 (18.4%)	7.1 (4) / 29 (19.5%)	7.4 (3.5) / 21 (17%)
Most frequent symptoms			
Fatigue and global deterioration	105 (38.6%)	63 (42%)	42 (34%)
Low grade fever (37-37.9ºC)	98 (36%)	63 (42%)	35 (28.5%) **(p=.04)**
Dyspnea	102 (37.5%)	74 (50%)	28 (23%) **(p<.001)**
Cough	94 (34.6%)	53 (36%)	41 (33%)
Anorexia	55 (20%)	27 (18%)	28 (23%)
Diarrhea	52 (19%)	26 (17.5%)	26 (21%)
Delirium	47 (17.3%)	29 (19.5%)	18 (15%)
High grade fever (≥38ºC)	45 (16.55)	25 (17%)	20 (16%)
Nausea/Vomiting	17 (6.3%) / 16 (5.9%)	13 (8.5%) / 11	4 (3.3%) / 5 (4%)
Sneezing-runny nose	10 (3.7%)	(7%)	1 (0.8%) **(p=.023)**
Fall(s)	7 (2.6%)	9 (6%)	3 (2.4%)
Ageusia / Anosmia	4 (1.5%) / 3(1.1%)	4 (2.7%)	2 (1.6%) / 1 (0.8%)

		2 (1.3%) / 2 (1.3%)	
Main biological parameters			
Hemoglobin (g/dL)	11.7 (2.3)	11.8 (2.1)	11.7 (2.4)
Leukocytes (nº/µL)	7862 (3903)	8910 (4300)	7021 (3300)**(**
Lymphocytes (nº/µL)	1262 (667)	1150 (657)	**p=.008)**
Platelets (nº/µL)	249000 (114000)	245000 (126000)	1353 (666)
D dimer	2231 (3932)	2529 (5000)	252000 (105000)
Creatinin (mg/dL)	1.34 (1.3)	1.49 (1.3)	1990 (2800)
ASAT	29 (26)	34 (31)	1.21 (1.3)
ALAT	23 (24)	29 (31)	25 (31)
Creatinin kinase	144 (412)	174 (295)	19 (14) **(p=.03)**
PCR	70 (97)	94 (94)	121 (484)
Ferritin (ng/mL)	456 (646)	660 (867)	50 (95) **(p=.012)**
			307 (357) **(p=.009)**

SD= standard deviation; Q1-Q3=quartile1-quartile3; Nº= number; %=percentage; MP=medicalization program; NL neurological; COPD chronic obstructive pulmonary disease; ASAT=aspartate aminotranspherase; ALAT=alanin aminoranspherase;

Table 3. Unadjusted differential complications and outcomes of affected residents during the medicalization program of four nursing homes with COVID-19 outbreaks in Seville, Spain.

PARAMETER (MEAN (SD)-MEDIAN [Q1-Q3] // N (%))	**GLOBAL (N=272)**	**PATIENTS DIAGNOSED WITH COVID-19 BEFORE MP (N=149)**	**PATIENTS DIAGNOSED WITH COVID-19 DURING MP (N=123) [OR; 95% CI]**
Patients with Complications	127 (47%)	83 (56%)	44 (36%) **p=.001 [0.4; 0.3-0.7]**
Acute respiratory failure	106 (39%)	74 (50%)	32 (26%) **p<.001[0.3; 0.2-0.6]**
Persistent or incidental delirium	36 (13%)	21 (14%)	15 (12%)
Immbility and 'bedridden syndrome'	32 (12%)	20 (13.7%)	12 (10%)
LRT bacterial infections	28 (10.3%)	14 (10%)	14 (11.5%)
Acute renal failure	19 (7%)	13 (9%)	6 (5%)
Oropharyngeal dysphagia	16 (6%)	10 (7%)	6 (5%)
Urinary tract infection	15 (5.5%)	8 (5.5%)	7 (5.7%)
Pressure ulcers	14 (5.1%)	9 (6%)	5 (4%)
Number of complications per patient	1.04(1.5)	1.25 (1.6)	0.8 (1.3) **p=.02**
Outcomes			
Composite end point*	234 (86%)	115 (77%)	119 (97%) **p<.001 [9; 3-25]**
Survival	211 (77.6%)	108 (72.5%)	103 (84%) **p=.03 [2; 1.1-3.5]**
Patients transferred to hospital	64 (23.5%)	43 (29%)	21 (17%) **p=.02 [0.5; 0.3-0.9]**
Transfers to Hospital per week	8 (8.5)	21.5 (2.1)	3.5 (1.9**) p=.02**

SD= standard deviation; Q1-Q3=quartile1-quartile3; Nº= number; %=percentage; MP=medicalization program; OR=odds ratio; CI= confidence interval; LRT= low respiratory tract; * Composite end -point of survival or optimal end-of-life care.

TABLE TITLES AND FIGURE CAPTIONS

Table 1. Global data of the four nursing homes' COVID-19 outbreaks in the city of Seville, Spain.

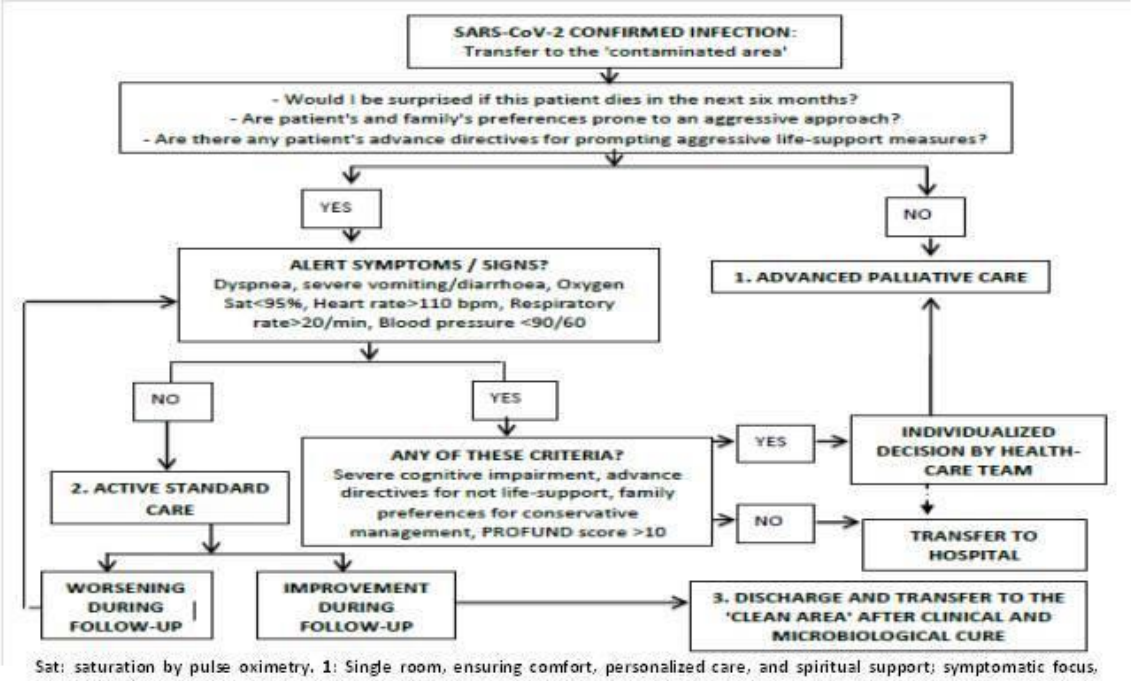
Table 2. Main clinical features of residents with COVID-19 during four nursing homes outbreaks in Seville, Spain.

Table 3. Unadjusted differential complications and outcomes of affected residents during the medicalization program of four nursing homes with COVID-19 outbreaks in Seville, Spain.

Figure 1. Main clinical algorithm for the clinical management of residents with SARS-CoV-2 infection during the medicalization program of four nursing homes with COVID-19 outbreaks.

Figure 2. Kaplan-Meier curve comparing survival of residents stratified to active standard care diagnosed before or during a medicalization program in four nursing homes of Seville (Spain) with SARS-CoV-2 outbreaks.

Figure 1



Sat: saturation by pulse oximetry. 1: Single room, ensuring comfort, personalized care, and spiritual support; symptomatic focus, oxygen therapy and antimicrobials if necessary; early detection of agony occurrence, palliative sedation and family accompaniment offer. 2: Antiviral, adjuvant and eventually antimicrobial treatment; daily measurement of vital signs, and clinical follow-up; parenteral and oxygen therapies, blood chemistry, and point of care ultrasonography if necessary. 3: Clinical cure=after three days of being asymptomatic; microbiological cure=clinical cure plus a control negative nasopharyngeal swab PCR; all patients were isolated in the 'contaminated area' for 14 days after being asymptomatic, and then, were performed a control nasopharyngeal swab PCR before transfer to the 'clean area'.

Figure 2