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ORIGINAL ARTICLE

Comorbidities and biomarkers associated with severity in hospitalized patients with COVID-19

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Abstract

Objective: The objective of the study was to evaluate clinical characteristics and analytical abnormalities at admission in hospitalized patients with COVID-19 and to identify which are associated with severe disease. **Methods:** A retrospective cohort study was performed. All adult patients admitted with COVID-19 from March 1, 2020, to May 31, 2020, were included consecutively. A descriptive analysis of clinical characteristics and analytical abnormalities at admission was made. We evaluated what comorbidities and biomarkers are associated with severe COVID-19 using a binary logistic regression model. **Results:** A total of 336 patients were included, 83 patients (24.7%) with severe disease. In patients with severe COVID-19, 76% were male, mean age was 71 years, and the most prevalent comorbidities were hypertension (57.8%), obesity (55.4%), dyslipidemia (50.6%), and diabetes (42.2%). In multivariate analysis, age (OR: 1.03; 95% CI 1.01-1.05; p = 0.004), male sex (OR: 2.92; 95% CI 1.62-5.27; p < 0.001), obesity (OR: 1.84; 95% CI 1.06-3.20; p = 0.030), and obstructive sleep apnea (OSA) (OR: 5.41; 95% CI 1.63-17.94; p = 0.006) were identified as comorbidities associated with severity. Patients with severe disease presented a lower arterial partial pressure of oxygen fraction and a greater inflammatory response at admission. Biomarkers associated with severe COVID-19 were lactate dehydrogenase (LDH) > 600 U/L (OR: 2.35; 95% CI 1.10-5.04; p = 0.027), serum ferritin > 600 mcg/L (OR: 2.66; 95% CI 1.24-5.70; p = 0.012), and interleukin-6 (IL-6) > 40 pg/mL (OR: 4.30; 95% CI 2.04-9.04; p < 0.001). **Conclusions:** Patients with severe COVID-19 disease present more comorbidities and inflammatory response at admission. Age, male sex, obesity, and OSA are associated with severity. Biomarkers at admission associated with severe COVID-19 are LDH > 600 U/L, serum ferritin > 500 mcg/L, and IL-6 > 40 pg/mL.

Keywords: Comorbidity. Biomarkers. COVID-19. Severity.

Introduction

Since the rising of the first cases of infection by a new strain of coronavirus (severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2) in December 2019 in Wuhan (China), the number of cases has increased all over the world. Spain is one of the most affected countries by SARS-CoV-2; on January 29, 2021, there were 2,743,119 COVID-19 cases with 58,319 deaths[1]. Clinical spectrum is broad, from asymptomatic patients to severe disease characterized by interstitial pneumonia and acute respiratory distress syndrome (ARDS) in 20% of patients[2,3]. Between 20 and 30% of

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individuals can progress to multiorgan dysfunction and death, especially elder people or with comorbidities[4-7].

Some analytical abnormalities have been noticed in patients with infection by SARS-CoV-2[8-12]. One of the mechanisms involved in this disease is activation of inflammatory cascade, leading to damage of microvascular system and activation of coagulation system. Related with that, some inflammatory, coagulation, or heart injury biomarkers are significantly elevated in individuals with severe COVID-19[13].

Identification of biomarkers able to differentiate between severe and not severe disease or recognition of patients with high mortality risk could allow a better risk stratification and an early and adequate attention of critically ill individuals.

The aim of our study is to know clinical characteristics and analytical abnormalities at admission in hospitalized patients with COVID-19 in our area, and to identify which of them are associated to severe disease.

Material and methods

Type of study

A retrospective cohort study was performed in a 1395 beds hospital with intensive care unit (ICU) and transplants unit, with a reference population of 384,852 inhabitants in the northwest of Spain. Admitted patients with diagnosis of infection by SARS-CoV-2 have been included consecutively from March 1, 2020, to May 31, 2020. All patients have been followed until 30 days after discharge or death.

Patients

Inclusion criteria were as follows: all patients > 18 years old discharged or dead after admission with confirmed infection by SARS-CoV-2. COVID-19 was confirmed by a positive test of proteinase chain reaction in real time (RT-PCR) in a respiratory sample or by a positive result of serologic test with suggestive symptoms. Exclusion criteria were as follows: subsequent admissions of the same patient, absence of informed consent, or asymptomatic patients with COVID-19 admitted for another cause.

Patients were classified into two groups: (1) severe COVID-19 including death, need of invasive mechanical ventilation (IMV), non-invasive mechanical ventilation (NIMV), high-flow nasal cannula (HFNC), admission on ICU, or arterial partial pressure of oxygen/inspired oxygen fraction (PaO_2/FiO_2) lower than 200 mmHg during hospitalization, and (2) non-severe COVID-19 (includes rest of patients).

Data collecting

By revision of clinical records of the patients, the following variables were gathered: (1) demographic data, (2) toxic habits, (3) Charlson Comorbidity Index and comorbidities, (4) symptoms and findings on physical exploration at admission, (5) laboratory data and radiological findings in the first 24 h of admission, (6) PaO_2/FiO_2 measurement by blood gas analysis or extrapolated by oxygen saturation ($SatO_2$) at admission and during hospitalization (in patients with clinical or respiratory impairment), (7) need of admission in ICU, IMV, or NIMV during hospitalization, (8) pharmacological treatment: previous and during hospitalization, and (9) days of hospital stay, ICU stay, and evolution.

To evaluate the comorbidity degree, we used Charlson Comorbidity Index[14]. Ischemic cardiopathy has been defined as the presence of myocardial infarction, angina, acute coronary syndrome, or coronary revascularization; cerebrovascular disease was defined as ischemic or hemorrhagic stroke or transient ischemic attack. It was considered a diagnosis of peripheral arterial disease in the presence of intermittent claudication, revascularization, limb amputation, or abdominal aortic aneurysm. Diagnosis of active neoplasm included solid or hematological tumors, active or diagnosed in the past 5 years, excluding melanoma. Chronic kidney disease (CKD) was defined as a glomerular filtrate < 45 mL/1.73 m^2 according to the CKD Epidemiology Collaboration equation[15]. ARDS classification was used according to Berlin definition[16].

Statistical analysis

Absolute values (n) and percentages (%) were calculated for categorical variables. The comparison of these variables among the groups was performed by Pearson's Chi-square test or Fisher's exact test. Association degree was estimated by odds ratio (OR) with a confidence interval of 95 (95% CI). Quantitative variables have been expressed as mean ± standard deviation (median). Kolmogorov–Smirnov test was utilized to analyze normality of parameter distribution. Comparison of quantitative variables was performed by Student's t-test (for variables with normal distribution) or Mann–Whitney-Wilcoxon test (for variables with non-normal distribution). Then, we proceed to

dichotomize those laboratory parameters with higher significant differences ($p \leq 0.001$) in univariate analysis. Receiver operating characteristic (ROC) curves were performed for those variables. Youden index was used to establish cutoff points for each laboratory variable in which ROC curve was maximized. A binary logistic regression analysis (forward procedure according to verisimilitude rate) was performed to assess the association of comorbidities and dichotomized biomarkers with severe disease separately. Severe COVID-19 was assigned as dependent variable, and all comorbidities and dichotomized laboratory variables with significant differences in univariate analysis were assigned as independent variables. Those variables with missing values above 25% of patients were excluded from the analysis. The missing data were handled by deletion.

Statistical analysis was performed using the program Statistical Package for the Social Sciences for Windows version 18.0.

Ethical and legal aspects

Personal data were treated in strict compliance with Law 14/2007 of July 3, on Biomedical Research, as well as Regulation (EU) 2016/679, of the European Parliament and of the Council, of April 27, 2016, on the protection of natural persons with regard to the processing of personal data and the free circulation of said data, and by which repeals Directive 95/46 EC (General Data Protection Regulation); and Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights. The data of this study are part of the SEMI-COVID-19 registry that has been approved by the provincial Research Ethics Committee of Malaga (Spain) as well as the ethics committee of our hospital.

Informed consent was requested from the patients. When it was not possible to obtain it in writing due to biosafety reasons or because the patient was already discharged from hospital, verbal informed consent was requested and noted on the medical record.

Results

General characteristics

During the study period, 1735 individuals were infected by COVID-19 of whom 336 (19.3%) were admitted. Most of them were diagnosed by RT-PCR (94.3%) in nasopharyngeal swab of which 17% presented a negative result in the first sample collected, being confirmed in further samples. Rest of patients were diagnosed by positive result of serologic test. Infection was nosocomial in 12.5% of cases; only 5.4% were health workers. A previous contact with SARS-CoV-2 was reported in 55%. Mean age was 66 ± 14 years old (being 58.6% older than 65 years of age), 58% were male, and Charlson Comorbidity Index was 1. Most patients had no toxic habits. Comorbidities were present in 83.6% of patients being the most prevalent: hypertension (48.5%), dyslipidemia (46.4%), diabetes (25.3%), obesity (38.4%), cardiopathy (19.6%), chronic pulmonary disease (15.8%), or neoplasm (11.9%). At admission, average duration of symptoms was 7 days, being more frequent fever, cough, asthenia, and dyspnea, this last one present in half of cases. PaO_2/FiO_2 was measured by blood gas analysis in 277 patients and by $SatO_2$ in 59 ($SatO_2$ > 92%, 52 in room air and seven with oxygen therapy) and ARDS was presented in 35% of patients at admission. During their evolution, 71% of patients presented ARDS (40% mild, 15% moderate, and 17% severe). In relation to severity, one-fourth of patients presented severe COVID-19 (83 patients) of which 44 (13.1%) needed attention in ICU; HFNC was required in 18 patients (5.4%), NIMV in 5 patients (1.5%), and IMV in 33 patients (10%) with a mean time of 18 days. The number of deaths during hospitalization was 52 patients (15.5%); only five cases died due to different causes.

Therapeutic management was determined according to the current protocol established in our center. Most used treatments were hydroxychloroquine (95%) and lopinavir/ritonavir (76.5%). Corticosteroids (35.4%) and tocilizumab (10.7%) were mainly utilized in severe cases. Other treatments such as B-interferon (3.3%), remdesivir (0.6%), anakinra (0.65%), or convalescent plasma (0.3%) were seldom employed in this period.

Comorbidities associated to severe COVID-19 disease

Table 1 shows clinical characteristics and comorbidities of patients according to severity. Severe COVID-19 disease was present in 25% (83 patients during hospitalization), most of them were male (75.9%) with higher mean age (71 vs. 65 years old), being more remarkable in over 65 age group (61 of 83 patients), where an increase of severity was clearly observed. Alcohol consumption was also associated with more severity but there were no significant differences in relation to smoking habits. The average of time between symptoms onset and admission was similar in both groups

Table 1. Clinical characteristics and comorbidities of patients included in the study, according to COVID-19 severity

Variables	Total	Non-severe	Severe	Univariate analysis		
	n (%)	n (%)	n (%)	OR	95% CI	p-value
Male	195 (58.0)	132 (52.2)	63 (75.9)	2.88	1.64-5.05	**< 0.001**
Age (average ± SD)	76 ± 14 (68)	65 ± 13 (67)	71 ± 12 (73)	1.03	1.01-1.05	**< 0.001**
Alcohol	25 (7.4)	15 (5.9)	10 (12.0)	2.17	0.93-5.04	0.065
Tobacco	15 (4.5)	14 (5.5)	1 (1.2)	0.54	0.11-2.50	0.532
Comorbidity						
Hypertension	163 (48.5)	115 (45.5)	48 (57.8)	1.64	0.99-2.71	0.050
Dyslipidemia	156 (46.4)	114 (45.1)	42 (50.6)	1.24	0.76-2.05	0.380
Diabetes	85 (25.3)	63 (24.9)	40 (48.2)	2.20	1.67-4.70	**< 0.001**
Obesity	129 (38.4)	83 (32.8)	46 (55.4)	2.54	1.53-4.22	**< 0.001**
Depression/anxiety	50 (14.9)	36 (14.2)	14 (16.9)	1.22	0.62-2.40	0.558
Neurodegenerative disease	23 (6.8)	16 (6.3)	7 (8.4)	1.36	0.54-3.44	0.509
Cardiopathy	66 (19.6)	39 (15.4)	27 (32.5)	2.64	1.49-4.68	**0.001**
Cerebrovascular disease	20 (6.0)	13 (5.1)	7 (8.4)	1.70	0.65-4.41	0.288
Peripheral vascular disease	24 (7.1)	15 (5.9)	9 (10.8)	1.93	0.81-4.59	0.131
Chronic lung disease	53 (15.8)	37 (14.6)	16 (19.3)	1.39	0.73-2.66	0.313
Chronic liver disease	13 (3.9)	9 (3.6)	4 (4.8)	1.37	0.41-4.58	0.743
Chronic kidney disease	15 (4.5)	10 (4.0)	5 (6.0)	1.55	0.51-4.69	0.539
Active neoplasm	40 (11.9)	23 (9.1)	17 (20.5)	2.57	1.30-5.10	**0.005**
Connective pathologies	17 (5.1)	11 (4.3)	6 (7.2)	1.71	0.61-4.78	0.384
Cardiopathy						
Ischemic cardiopathy	36 (10.7)	25 (9.9)	11 (13.3)	1.39	0.65-2.97	0.389
Congestive heart failure	20 (6.0)	8 (3.2)	12 (14.5)	5.17	2.03-12.15	**0.001**
Atrial fibrillation	34 (10.1)	17 (6.7)	17 (20.5)	3.57	1.73-7.38	**< 0.001**
Chronic lung disease						
COPD	20 (6.0)	13 (5.1)	7 (8.4)	1.70	0.65-4.41	0.288
Asthma	25 (7.4)	20 (7.9)	5 (6.0)	0.74	0.27-2.05	0.571
OSA	16 (4.8)	5 (2.0)	11 (13.3)	7.57	2.55-22.52	**< 0.001**
Total	336	253	83			

n: number; OR: odds ratio; CI: confidence interval; SD: standard deviation; COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnea.
Bold p-values are those with statistical significances.

(7 vs. 6 days, p = 0.053), being dyspnea the most frequent symptom in severe cases and diarrhea the one more frequent in non-severe cases. At admission, 78.7% of patients presented radiological findings suggestive of pneumonia, increasing this percentage to 88.6% during hospitalization. According to analyzed comorbidities, patients with severe disease presented more frequently diabetes (48.2 vs. 24.9%, p < 0.001), obesity (55.4 vs. 32.8%, p < 0.001), cardiopathy (32.5 vs. 15.4%, p = 0.001), obstructive sleep apnea (OSA) (13.3 vs. 2%, p < 0.001), and neoplasm (20.5 vs. 9.1%, p = 0.005). In relation to cardiopathy, we have observed that these differences were due to prevalence of congestive heart failure and atrial fibrillation without differences in ischemic cardiopathy. No significant differences were observed in the rest of comorbidities.

When multivariate analysis was performed, only four variables were independently associated with severity of disease: age (OR: 1.03; 95% CI 1.01-1.05; p = 0.004), male sex (OR: 2.92; 95% CI 1.62-5.27; p < 0.001), obesity (OR: 1.84; 95% CI 1.06-3.20; p = 0.030), and OSA (OR: 5.41; 95% CI 1.63-17.94; p = 0.006) (Table 2).

Biomarkers associated to severe COVID-19 disease

Analytical data of patients with severe and non-severe disease at admission are shown in Table 3. Significant differences have been identified between both groups in hematological parameters: higher leukocyte count (median 6680 vs. 5230 × 10^6/L, p = 0.003), lymphopenia (635 vs. 1030 × 10^6/L, p < 0.001), and lower platelet count (163 vs. 185 × 10^9/L, p = 0.021) were observed in severe patients. In relation to biochemical parameters, patients with severe COVID-19 disease presented higher values of basal glycemia, creatinine, aspartate

Table 2. Comorbidities included in multivariate analysis to predict COVID-19 severity

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Obesity	2.54	1.53-4.22	< 0.001	1.84	1.06-3.20	0.030
Active neoplasm	2.57	1.30-5.10	0.005			
Cardiopathy	2.05	1.20-3.49	0.008			
Diabetes	2.20	1.67-4.70	< 0.001			
OSA	7.57	2.55-22.52	< 0.001	5.41	1.63-17.94	0.006
Male sex	2.88	1.64-5.05	< 0.001	2.92	1.62-5.27	< 0.001
Age	1.03	1.01-1.05	< 0.001	1.03	1.01-1.05	0.004

OR: odds ratio; CI: confidence interval; OSA: obstructive sleep apnea.
In relation to age, OR is modified for each year.

Table 3. Analytical data at admission of patients included in the study, according to COVID-19 severity

Variables	Missing	Total	Non-severe	Severe	p-value
Symptom onset time (days)	0	7 ± 5 (7)	7 ± 5 (7)	6 ± 4 (6)	0.011
PaO_2/FiO_2	0	308 ± 84 (309)	329 ± 74 (326)	251 ± 87 (246)	< 0.001
PaO_2/FiO_2<300 mmHg	0	118 (35.1)	64 (25.3)	54 (65.1)	< 0.001
PaO_2, mmHg	59	68.7 ± 17.3 (66.7)	71.2 ± 15.7 (69)	60.7 ± 18.8 (60.4)	< 0.001
$PaCO_2$, mmHg	59	33.2 ± 5.9 (33.0)	33.3 ± 5.3 (33.0)	32.7 ± 7.2 (32.0)	0.251
Lactate, mmol/L	59	1.3 ± 0.6 (1.2)	1.2 ± 0.4 (1.1)	1.7 ± 0.9 (1.4)	< 0.001
Analytical parameters					
Hemoglobin, g/dL	1	13.2 ± 1.7 (13.6)	13.3 ± 1.8 (13.5)	12.8 ± 2.2 (12.9)	0.133
Leukocyte count, 10^6/L	1	6268 ± 3050 (5530)	5904 ± 2373 (5230)	7392 ± 4376 (6680)	0.003
Lymphocyte count, 10^6/L	1	1124 ± 1212 (920)	1150 ± 650 (1030)	1046 ± 2177 (635)	< 0.001
Platelet count, 10^9/L	1	203 ± 95 (180)	208 ± 95 (185)	188 ± 195 (163)	0.021
Glucose, mg/dL	2	115 ± 39 (104)	109 ± 35 (100)	119 ± 41 (112)	0.003
Creatinine, mg/dL	1	1.3 ± 0.7 (0.9)	1.0 ± 0.5 (0.8)	1.4 ± 1.1 (1.1)	**< 0.001**
Sodium, mmol/L	1	136 ± 3 (137)	136 ± 3 (137)	136 ± 5 (136)	0.139
Albumin, g/dL	12	3.6 ± 0.5 (3.6)	3.6 ± 0.5 (3.7)	3.3 ± 0.5 (3.4)	**< 0.001**
ALT, U/L	3	41 ± 30 (33)	39 ± 30 (31)	47 ± 31 (39)	**0.001**
AST, U/L	6	41 ± 34 (33)	41 ± 36 (32)	41 ± 28 (34)	0.958
Creatine kinase, U/L	23	126 ± 162 (74)	105 ± 124 (67)	194 ± 243 (123)	**0.001**
Troponin I, mcg/L	38	0.06 ± 0.25 (0.01)	0.039 ± 0.107 (0.017)	0.089 ± 0.344 (0.017)	0.007
Procalcitonin, ng/mL	8	0.92 ± 7.54 (0.10)	0.17 ± 0.33 (0.09)	2.45 ± 10.75 (0.16)	**< 0.001**
C-reactive protein, mg/L	14	67.8 ± 67.5 (47.1)	60.5 ± 59.0 (41.3)	90.4 ± 85.4 (67.7)	**0.001**
Lactate dehydrogenase, U/L	18	521 ± 268 (462)	487 ± 249 (439)	628 ± 298 (618)	**< 0.001**
Serum ferritin, mcg/L	42	679 ± 815 (432)	587 ± 732 (405)	1056 ± 1014 (757)	**< 0.001**
Interleukin-6, pg/mL	50	57.2 ± 147.6 (23.6)	37.9 ± 69.6 (21.3)	143.7 ± 298.6 (52.3)	**< 0.001**
D-dimer, ng/mL	10	1752 ± 7508 (683)	1143 ± 1560 (644)	3786 ± 15095 (763)	0.046
Total		336	253	83	

Data are presented as mean ± standard deviation (median).
Bold p-values are those included in multivarite analysis.
PaO_2/FiO_2: arterial partial pressure of oxygen/inspired oxygen fraction;
PaO_2: arterial partial pressure of oxygen;
$PaCO_2$: arterial partial pressure of carbon dioxide;
ALT: alanine aminotransferase; AST: aspartate aminotransferase.

aminotransferase, creatine kinase, and troponin I while albumin levels were lower. Inflammation-related markers were also analyzed and an increased inflammatory response was observed in patients with severe disease.

Table 4. Dichotomized laboratory parameters included in multivariate analysis to predict severe COVID-19 disease

Variables	Univariate analysis					Multivariate analysis		
	Non-severe (n = 253)	Severe (n = 83)	OR	95% CI	p-value	OR	95% CI	p-value
Lymphopenia (< 700×10^6/L)	55 (21.7)	44 (53.7)	4.16	2.46-7.06	< 0.001			
Creatinine > 1.5 mg/dL	23 (9.1)	21 (25.6)	3.44	1.78-6.63	< 0.001			
Albumin < 3.4 mg/dL	63 (25.8)	38 (47.5)	2.59	1.53-4.39	< 0.001			
Hepatitis (ALT > 50 or AST > 37 U/L)	90 (35.9)	45 (54.9)	2.17	1.31-3.60	0.002			
Creatine kinase > 190 U/L	26 (10.9)	20 (26.7)	2.96	2.55-22.52	< 0.001			
C-reactive protein > 40 mg/L	122 (50.2)	56 (70.9)	2.41	1.39-4.17	0.001			
Procalcitonin > 0.07 ng/mL	144 (57.8)	71 (89.9)	6.47	2.98-14.01	< 0.001			
LDH > 600 U/L	50 (20.7)	40 (52.6)	4.26	2.46-7.37	< 0.001	2.35	1.10-5.04	0.027
Serum ferritin > 600 mcg/L	61 (29.0)	32 (61.5)	3.90	2.07-7.36	< 0.001	2.66	1.24-5.70	0.012
Interleukin-6 > 40 pg/mL	47 (24.5)	29 (65.9)	5.96	1.69-6.03	< 0.001	4.30	2.04-9.04	< 0.001

n: number; OR: odds ratio; CI: confidence interval; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase.

Furthermore, it has been showed higher levels of C-reactive protein (CRP) (67.7 vs. 43.8 mg/L, p = 0.001), lactate dehydrogenase (LDH) (618 vs. 439 U/L, p < 0.001), serum ferritin (757 vs. 405 mcg/L, p < 0.001), interleukin-6 (IL-6) (52 vs. 21 pg/mL, p < 0.001), D-dimer (763 vs. 644 ng/mL, p = 0.046), and procalcitonin (0.16 vs. 0.09 ng/mL, p < 0.001), in patients with severe disease.

A multivariate analysis was performed using the presence of severe COVID-19 as dependent variable and those dichotomized biomarkers with statistical signification (p ≤ 0.001) in previous univariate analysis as independent variables. It has been observed that LDH > 600 U/L (OR: 2.35; 95% CI 1.10-5.04; p = 0.027), serum ferritin > 600 mcg/L (OR: 2.66; 95% CI 1.24-5.70; p = 0.012), and IL-6 > 40 pg/mL (OR: 4.30; 95% CI 2.04-9.04; p < 0.001) were independently related with severity of SARS-CoV-2 (Table 4).

ROC plot of biomarkers associated to severity of COVID-19 in multivariate analysis is shown in figure 1; area under the curve, sensitivity, and specificity are reflected on table 5.

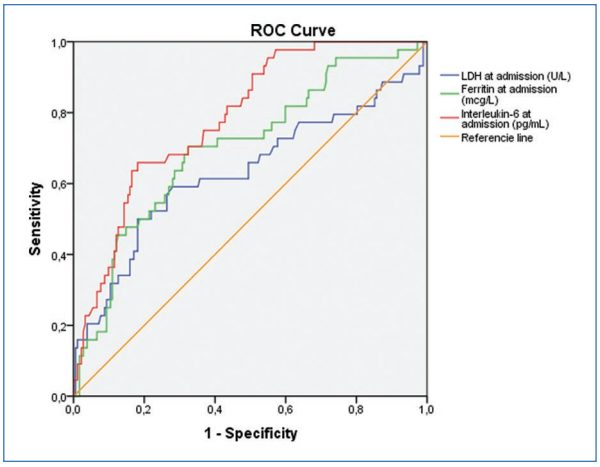

Figure 1. ROC curve of analytical parameters associated to severe COVID-19 disease.
LDH: lactate dehydrogenase.

Discussion

SARS-CoV-2 pandemic has supposed an unprecedented challenge and a great overburden for all health systems. It is notable that percentage of admissions in our area (19.3%) was lower than other areas of Spain[1].

We think that they may be due to our geographical location with more dispersed population and confinement measures in place. It is important to know the characteristics of patients with COVID-19 who present a poor development to optimize their medical care and distribution of resources. In our study, we have identified significant differences in some comorbidities and laboratory parameters between patients with severe and non-severe COVID-19. It can help us to identify patients with increased risk of developing severe disease so that they could be submitted to close monitoring or earlier treatment.

Table 5. Area under the curve of analytical parameters associated to severe COVID-19 disease

Variables	AUC	95% CI	p-value	Cutoff point	Sensibility	Specificity
LDH	0.632	0.527-0.737	< 0.001	600 U/L	52.6%	79.3%
Serum ferritin	0.702	0.614-0.790	< 0.001	600 mcg/L	61.5%	71.0%
Interleukin-6	0.787	0.719-0.855	< 0.001	40 pg/mL	65.9%	75.5%

AUC: area under the curve; CI: confidence interval; LDH: lactate dehydrogenase.

Our study shows that age and male sex are associated with severe COVID-19. It includes mainly male and elderly patients with a high comorbidity (84%) being higher than some Chinese series, but similar to other European series[6,17]. Hypertension, diabetes, dyslipidemia, and obesity were the most frequent comorbidities, similar to other series[4,18,19]. In-hospital mortality in the present study (15.5%) resembles other Spanish series, but it is lower than those of Wuhan[17,18].

On the other hand, in our series, a quarter of patients presented a severe disease by SARS-CoV-2, being the literature data very inconsistent[13]. It is noticeable the high percentage of male patients in severe disease group (three-quarters in the present study) and people over 65 years old which agree with the higher mortality found in those patients in other series[19,20].

We have found no differences in time between onset of symptoms and admission, so severity cannot be attributed to a delay in medical care. In our study, most of severe patients reported respiratory symptoms and non-severe patients digestive symptoms. It seems to indicate that lung affectation is present in the development of severity early.

Several comorbidities such as diabetes, obesity, neoplasm, OSA, and cardiopathy are associated to poor prognosis in literature[21-23]. However, in our series, only obesity and OSA showed significant differences in multivariate analysis.

Attempts have been made to identify analytical parameters or biomarkers related with a better or poor prognosis[24]. In our study, we have found that severe patients presented higher leukocytes levels. It could be related with bacterial coinfections, presence of higher viral load, cytokine storm induced by SARS-CoV-2, or use of higher doses of corticosteroids employed in severe patients. Furthermore, lymphopenia (defined as lymphocytes < 700 × 10^6/L) was associated to severe disease in univariate analysis. However, these differences were not presented in multivariate analysis, unlike other published series[25,26]. It is thought that invasion produced by viral particles of SARS-CoV-2 damages the cytoplasmic component of lymphocyte and causes its destruction. Furthermore, lymphopenia is also common in severe patients with infection by other coronaviruses like MERS. Thus, as some authors suggest probably that phenomenon also produces lymphopenia in severe patients with SARS-CoV-2[13,27].

Likewise, we have found higher levels of glucose or creatinine that could be related with low perfusion and hypovolemia. It was also observed lower levels of albumin which leads us to think that severe patients have a bigger degree of malnutrition. As in other series, we also have found an association between severity and levels of D-dimer what indicate a procoagulant status in infection by SARS-CoV-2, although the cause has not cleared yet[25]. In our series, all these differences were observed in univariate but not in multivariate analysis.

In relation to inflammatory biomarkers, we have observed significant differences in levels of CRP, LDH, ferritin, and IL-6 according to severity. These findings have also been described in other studies[22,28,29]. Exaggerated inflammatory response can lead to "cytokine storm" that may be the booster of acute lung injury and ARDS, and thus conduct to other tissue damages and multiorgan failure[30]. Probably, the high levels of these markers can help to make decisions about need of admission or beginning therapies with corticosteroids and other immunomodulators.

Finally, after identifying those laboratory parameters with statistical signification, we dichotomized them to set a cutoff point above of it the disease may be more severe. In our series, we observed that ferritin > 600 mcg/L, LDH > 600 U/L, and IL-6 > 40 pg/mL are independently associated to severe COVID-19 disease. It could be interesting to check if these values are comparable to other series, because in affirmative case, they could be used to create severity scales or even clinical practice guidelines.

Strengths and limitations

Our study presents the limitations inherent to a retrospective study whose results depend on the quality of data gathered by different researchers. Besides, the study is single center and results cannot be extrapolated to general population because it can be local biases. Perhaps, one of the most important limitations is the diversity of employed treatments, consequence of frequent changes in protocols: this fact makes complicated to identify risk factors of mortality, due to biases. Furthermore, the low number of events in some of comorbidity variables may limit the results by excluding potential prognostic variables for being too little. Perhaps, this may be solved by sub-analysis of different populations in multicenter studies.

As strengths, we should underline that the size of the series is substantial and its characteristics are similar to the majority of European series. Furthermore, explored variables are comorbidities and analytical parameters easy to obtain in clinical history without need of invasive procedures.

Conclusions

In hospitalized patients with COVID-19, those who develop severe disease have more comorbidities and higher inflammatory response at admission. Age, male sex, obesity, and OSA are associated to severity. Analytical parameters such as LDH > 600 U/L, ferritin > 600 mcg/L, and IL-6 > 40 pg/mL can help us to identify patients who are likely to develop severe disease.

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Conflicts of interest

The authors declare that they have no relevant financial or non-financial interests to disclose.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that we have followed the protocols of our work center on the publication of patient data. The data of this study are part of the SEMI-COVID-19 registry that has been approved by the provincial Research Ethics Committee of Malaga (Spain), as well as the ethics committee of our hospital.

Right to privacy and informed consent. The authors declare that no patient data appear in this article. Informed consent was obtained from all individual participants included in the study.

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ORIGINAL ARTICLE

Prevalence of cardiac amyloidosis in Spanish patients with heart failure: The PREVAMIC study design

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Abstract

Introduction: Cardiac amyloidosis (CA) has been considered a rare disease, but different studies show that its prevalence is higher than previously thought. Previous studies carried out on the prevalence of CA are heterogeneous and provide inconclusive and changing data over time that do not allow us to know the real prevalence of this pathology. In Spain, 60% of patients with heart failure (HF) admitted to hospitals are cared for in Internal Medicine Services, and their follow-up is carried out by internists, but there are no prevalence studies in this type of Internal Medicine patients. The PREVAMIC is a study designed by the HF Working Group of the Spanish Society of Internal Medicine to known the Prevalence of CA in HF patients cared by internists. **Objectives:** The main objective is to estimate the prevalence of different types of CA in patients with HF, aged 65 years and older, with left ventricular hypertrophy, managed in Internal Medicine departments. Secondary objectives are to describe clinical, laboratory, and echocardiographic features of patients with CA and to compare 1-year readmissions and mortality rates in patients with and without CA. **Methods:** A multicenter, observational, cross-sectional, prospective, cohort study with a 1-year follow-up. Inclusion criteria: Inpatients or outpatients with HF, aged ≥ 65 years, both genders, with septum or posterior wall > 12 mm, under the care of internists. **Conclusions:** Our prospective investigation study aims to improve knowledge about the prevalence of CA in patients with HF treated in the Internal Medicine setting.

Keywords: Cardiac amyloidosis. Heart failure. Prevalence.

Introduction

Cardiac amyloidosis (CA) has been considered a rare disease, but different studies show that its prevalence is higher than previously thought[1]. Various types of amyloid can infiltrate cardiac tissue, but in 90-95% of CA cases, it is transthyretin amyloidosis (ATTR), in its wild-type or senile (ATTRwt) and hereditary (ATTRv) varieties, or primary amyloidosis (AL)[2-6]. It is known that around 25% of octogenarians show signs of TTR deposits at autopsy[7]. More recent studies have identified ATTR in up to 5% of patients with hypertrophic cardiomyopathy, in 13% of patients with heart failure (HF) with left ventricular preserved ejection fraction (HFpEF), and in 6-15% of patients with aortic stenosis[8-14]. However, ATTR cardiomyopathy is an underdiagnosed entity because it requires a high index

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of suspicion, and early diagnosis is of great importance to offer patients the most appropriate therapy[15].

The studies carried out on the prevalence of CA are heterogenous in their design and provide inconclusive data that do not allow us to know the real prevalence of this pathology. In addition, ATTR-CA can present different prevalence for geographical reasons, since the hereditary form is concentrated in endemic foci[16].

In Spain, 60% of patients with HF admitted to hospitals are cared for in Internal Medicine Services[17-19], but there are no prevalence studies in these patients.

An opportunity to carry out new prevalence studies has been provided by the existence of non-invasive methods for the diagnosis of ATTR based on performing a scintigraphy with ^{99m}Tc-DPD/PYP/HMDP, showing positive uptake, and absence of monoclonal protein detectable by immunofixation in blood and urine[20].

Another justification for our study is that there are new treatment options[21] among which Tafamidis has recently seen its efficacy in treating ATTRwt cardiomyopathy[22]. Others such as Patisiran[23] and Inotersen[24] are effective drugs in ATTRv but given that they are high-priced drugs, a prevalence study can help estimate the real healthcare cost of this disease.

For these reasons, the HF and Atrial Fibrillation Working Group of the Spanish Society of Internal Medicine decided to carry out a study to estimate the current prevalence of different types of CA in patients with HF treated in the Internal Medicine setting.

Objectives

The main objective of the study is to estimate the present prevalence of different types of CA in patients with HF, aged ≥ 65 years, with left ventricular hypertrophy (LVH) > 12 mm, and any left ventricular ejection fraction (LVEF) value, treated in the Internal Medicine setting. Secondary objectives are: (1) to describe and compare the clinical characteristics of patients with and without CA; (2) to describe and compare the analytical findings of patients with and without CA; (3) to describe and compare the electrocardiographic, echocardiographic and other studies findings in patients with and without CA; and (4) to compare the rates of readmissions and mortality in 1 year of patients with and without CA.

Methods

Design and study population

This is a nationwide, multicenter, observational, cross-sectional, prospective, cohort study with 1-year follow-up. Patients will be recruited from the Internal Medicine Departments of Spanish hospitals.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
– Age ≥ 65 years. Both genders – Inpatients or outpatients from the Internal Medicine Departments – Heart failure (2016 European Guideline criteria) – Heart failure symptoms – NYHA Class II to IV – Echocardiogram performed in the previous 24 months or at time of inclusion – Left ventricular ejection fraction: any value – Left ventricular hypertrophy: septum or posterior wall > 12 mm – Diuretic treatment in the last 6 months – NT-proBNP > 1600 or BNP > 400 in AHF, or NT-proBNP > 400 or BNP > 100 in a stable situation
Exclusion criteria
– Patients with oncological disease (if solid tumor) – Patients who are included in a clinical trial – Patients who refuse to participate

AHF: acute heart failure; BNP: brain natriuretic peptide; NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide; NYHA: New York Heart Association.

Patient selection and inclusion/exclusion criteria

The inclusion of patients will be done prospectively and consecutively. Each center will be assigned a minimum number of patients to include tailored to the size of the hospital. The start of recruitment will be simultaneous in all centers. Eligibility requirements included inpatients or outpatients from the Internal Medicine, an age of at least 65 years, any ejection fraction, and New York Heart Association (NYHA) class II to IV symptoms. Furthermore, patients were required to have an elevated plasma level of N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP). Only those patients who strictly meet the diagnostic criteria for HF of the Guidelines of European Society of Cardiology of 2016[25] and who have LVH (septum or posterior wall > 12 mm) will be included. The inclusion and exclusion criteria are detailed in table 1.

Study variables and data collection

The study consists of an inclusion visit and a 1-year follow-up visit. The study variables that will be collected at each visit are detailed in table 2. Data will be included in an electronic medical record accessed with a personal password. To preserve confidentiality, no personal data will be stored.

Table 2. Study variables at inclusion and follow-up visits

Inclusion visit	
Demographic/general variables	Age Gender Body mass index
HF-related variables	HF etiology NYHA scale Previous admissions for AHF Previous ED visits for AHF
Comorbidities	Relevant previous diseases Charlson Comorbidity Index
Functional/cognitive status	Barthel Index Pfeiffer test
Relevant data specific to amyloidosis	Presence of "red-flags" of amyloidosis
Symptoms, signs and clinical examination findings	Related to HF or amyloidosis
Laboratory parameters	Blood cell count Biochemical parameters* Natriuretic peptides Cardiac Troponin Carbohydrate antigen 125 Serum free light chain, serum and urine protein electrophoresis with immunofixation
Complementary procedures	Electrocardiogram Echocardiogram parameters Cardiac scintigraphy (^{99}mTc-DPD/PYP/HMDP) Cardiac MR (if performed) Biopsies (if performed)
Drugs	Baseline treatment Treatment after amyloidosis diagnosis
Genetic study	TTR gene mutations
One-year follow-up visit	
Outcomes	Vital status and causes of death Admissions for HF and other causes ED visits for HF and other causes

AHF: acute heart failure; ED: emergency departments; MR: magnetic resonance; NYHA: New York Heart Association; TTR: transthyretin: HF: heart failure.
*Including glucose, urea, creatinine, sodium, potassium, total proteins, bilirubin and liver enzymes.

Sample size

Choosing as the target population the annual discharges in Spain for HF in Internal Medicine, which are approximately 60,000, with an estimated prevalence of 10%, a confidence level of 95% and a precision of 3%, the calculated sample size is 382 patients.

Statistical analysis

Continuous variables will be expressed as the value of the mean and standard deviation or as median and interquartile range, depending on the normality of their distribution. Categorical variables will be expressed as percentages or rates. A descriptive analysis of the data will be carried out, calculating prevalence rates, and comparing different variables of interest for the objectives of the study.

The comparison will be made using the Chi-square test for categorical variables and Student's t-test for normal quantitative variables. For non-normal quantitative variables, the non-parametric U-Mann Whitney test will be used. Regarding the follow-up data, the association of different variables with readmission and mortality data will be assessed using univariate and multivariate analysis. An analysis of survival curves will also be performed using the Kaplan-Meier method using the log-rank test. Statistical significance will be considered a $p < 0.05$.

Ethical aspects

The study will be carried out in accordance with the Declaration of Helsinki and with the current Spanish laws on the Protection of Personal Data. An informed consent will be obtained from all participating subjects.

This study has been classified by the Spanish Agency for Medicines and Health Products as a "No post-authorization observational study;" has been approved by the Clinical Research Ethics Committee of the Virgen Macarena and Virgen del Rocío University Hospitals of Seville (Spain); and is registered on the website ClinicalTrials.gov with the number NCT04066452.

Study coordination and data audit will be performed by the Internal Medicine HF Unit, and by the Research and Innovation Units of the Virgen Macarena University Hospital of Seville, Spain.

Discussion

The main objective of the PREVAMIC study is to estimate the current prevalence of different types of CA in patients with HF treated in the Internal Medicine setting.

The studies carried out on the prevalence of CA are heterogeneous in their design, in the patient selection criteria, and in the medical specialty of the authors, and provide inconclusive that do not allow us to know precisely the prevalence of this pathology. Different

prevalence values have been described in heart diseases: 5% in patients with hypertrophic cardiomyopathy, 13% in patients with HF with HFpEF, and 6-15% in patients with aortic stenosis[8-14]. Although we now know that these prevalence values are significant, CA had been considered a rare disease, and because its diagnosis was complex and with few therapeutic options, it was underdiagnosed and was only treated in highly specialized units. However, the appearance of new, simple and affordable diagnostic algorithms[20], with the advances in cardiac imaging techniques, including nuclear cardiac scintigraphy, and the availability of new effective therapies[21,26] have aroused the interest in this pathology.

In Spain, the main cause of admission to Internal Medicine services is HF. More than 60,000 patients/year with HF are admitted to hospitals and cared for in the Internal Medicine Services[17-19], and the follow-up of these patients is carried out with increasing frequency by internists in specific Units such as those created through the UMIPIC program[27]. In general, Internal Medicine patients with HF compared to those attended by Cardiology are older, more frequently women and with a greater number of associated comorbidities and preserved LVEF[28,29], and there are no prevalence studies of CA in this type of patients.

Furthermore, the decision as to who, how and when to finance the treatment of this disease should be based on arguments of a humanistic nature (justice, equity), clinical (severity of the disease, availability of therapeutic alternatives, change in the course of the disease) and economic (opportunity cost, budget impact, system sustainability)[30], and since the new drugs to treat Amyloidosis, such as Tafamidis, Patisiran and Inotersen, are high-priced drugs, a prevalence study is currently of greater interest to estimate the real healthcare cost that this disease may imply for health agencies.

We consider that all these reasons justify carrying out this prevalence study in this type of Internal Medicine patients.

In conclusion, we design a prospective study that aims to improve knowledge about the prevalence and the clinical characteristics of patients with CA and HF treated in the Internal Medicine setting. It can also contribute to estimating the healthcare cost that this disease may imply.

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Conflicts of interests

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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STATEMENT OF THE SEMI

The hospital of today. The Oporto consensus

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Abstract

The evolution of society has led to big challenges for health-care systems. Sociological, demographic, epidemiological, healthcare, environmental, technological, and economic factors along with the development of innovative health-care technology make it necessary to rethink the model of providing healthcare and organizing hospitals. This consensus, called The Oporto Consensus, statement reflects the societies' views on the principal changes in hospital organization that will be necessary in upcoming years, especially changes in which internal medicine can and must play an important role. These changes could lead over 10 general principles that incorporate the changes related to the active incorporation of patients, climate change, the prevention of pandemics or alternatives to conventional hospitalization, or the existence of sufficient public funding. In the other hand, changes are necessary in the current model of organization of the health system, based on the integration of the different care levels, focused on processes, and patient-centered multidisciplinary teams, avoiding conventional hospitalization and promoting the use of new technologies in health care, among other. Hence, this document identifies the main challenges that health-care systems currently face and makes proposals for changes in hospital organization to respond to them. Both Spain and Portugal have seen good examples of innovative healthcare adapted to the populations' needs that take advantage of scientific advances and current technology. These proposals provide a starting point for discussions about how to better organize the health-care system to meet the population's changing health needs while guaranteeing equitable and sustainable care.

Keywords: Hospital organization. Internal medicine. Portugal. Societies. Medical. Spain.

Introduction

The evolution of society has led to big challenges for health-care systems. Sociological, demographic, epidemiological, healthcare, environmental, technological, and economic factors along with the development of innovative health-care technology make it necessary to rethink the model of providing healthcare and organizing hospitals.

In June 2021, the Portuguese Society of Internal Medicine and the Spanish Society of Internal Medicine debated this issue in depth at a meeting held in Oporto, Portugal. The creation of this document, called The Oporto Consensus, grew out of these discussions. This consensus statement reflects the societies' views on the principal changes in hospital organization that will be necessary in upcoming years, especially changes in which internal medicine can and must play an important role.

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General principles

1. The hospital of the future must respond to the population's needs and must incorporate the new values of citizenship.
2. Aging and multimorbidity require the creation of multidisciplinary teams that include professionals from different levels of care as well as a greater integration of these levels of care, including social welfare units.
3. Climate change is already affecting our patients and poses new challenges for health that must be addressed in the short-term.
4. The possible emergence of new pandemics makes it necessary to have emergency plans; equipment reserves; more flexible hospitals; greater investment in internal medicine; and better coordination among the various levels of care, including public health.
5. Greater equity in access to quality healthcare with a guarantee of compliance with response times suitable to patients' needs will be fundamental.
6. "Healthcare in your community" must be promoted as a way of creating alternatives to conventional hospitalization and bringing individualized care to communities.
7. The active participation of the patient and his or her caregivers in clinical decision-making must be fostered.
8. Strengthening health-care information and communication systems are fundamental to take advantage of the full potential of teleconsultations, telemonitoring, the variety of methods for contacting and interacting with patients and access to knowledge bases and shared medical records.
9. Hospital physicians must participate in disease prevention and health promotion campaigns.
10. Financial sustainability and the guarantee of equity in treatment are fundamental.

Changes in hospital organization

– Healthcare is provided through different levels of care that do not work together.
  • Healthcare must evolve towards integration among the hospital, primary care, public health, continuing care, and social welfare units with a single point of administration and financial management. Social support services must be provided at the same time as treatment for physical diseases.
– The current form of organization is based on a rigid departmental structure centered on the physician and the specialty.
  • A form of organization based on versatile structures or care areas organized around health-care processes must be created. The COVID-19 pandemic revealed the importance of simplifying processes with the creation of patient-centered multidisciplinary teams.
– Accessibility is restricted and based on appointments and rigid processes.
  • Communication between patients and primary care with the hospital must be facilitated, allowing for access to unscheduled consultations that prevent patients from having to consult in the emergency department.
– Complex chronic patients receive treatment when they have episodes — a discontinuous manner of providing care — and they must frequently resort to using the emergency department.
  • Case management programs based on individual care plans and the figure of a case manager are needed for complex chronic patients.
– Hospitalization is used excessively for patients with mild disease and for those undergoing diagnostic examinations.
  • Hospitalization must be reserved for severe cases and emphasis must be placed on home hospitalization and rapid diagnosis units.
– The majority of complications in patients who undergo surgery are medical problems.
  • Surgical departments must invest in comanagement programs with internal medicine and surgical specialty departments with views to improving outcomes in these patients.
– There is a high degree of health illiteracy. The patient and the family have a passive role in the health-care process.
  • The hospital must educate patients and their caregivers so that they form part of the health-care team, including in decision-making. Likewise, patient associations must be involved in health-care organization, including hospital care.
– The hospital has deficient technology for the exchange of clinical information with other units, the use of telemedicine, and the use of telemonitoring.
  • Digital innovation is key: medical records and test results that are accessible to patients, telemonitoring that allows for safe outpatient care, structured teleconsultation and consultation schedules for primary care, and the use of artificial intelligence tools applied to healthcare are needed.
– The hospital is eminently a place for treating disease and does not provide health education activities for the public.

  - Hospital medical departments must participate in healthy lifestyle and health literacy campaigns.
- Training for physicians almost exclusively aimed at providing healthcare, teaching, and research. Health management has largely been in the hands of non-medical managers.
  - Physicians must be trained and involved in management activities. Managers must be open to the opinions of health-care professionals and patients, without losing sight of the sustainability of the system.

Conclusion

This document identifies the main challenges that health-care systems currently face and makes proposals for changes in hospital organization to respond to them. Both Spain and Portugal have seen good examples of innovative healthcare adapted to the populations' needs that takes advantage of scientific advances and current technology. These proposals provide a starting point for discussions about how to better organize the health-care system to meet the population's changing health needs while guaranteeing equitable and sustainable care.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.