Title: The need for early management in patients with COVID-19

Authors: Audrey Giraud-Gatineau[1,2,3,4]; Sébastien Cortaredona[2]; Jean-Christophe Lagier[1,4]; Matthieu Million[1,4]; Philippe Brouqui[1;4]; Yolande Obadia; Patrick Peretti-Watel[2,6]; Didier Raoult; Stéphanie Gentile[7]

Affiliations:

[1] IHU Méditerranée Infection, 19-21 boulevard Jean Moulin, 13005 Marseille, France;

[2] Aix Marseille Univ, Institut de Recherche pour le Développement (IRD), Assistance Publique - Hôpitaux de Marseille (AP-HM), Service de Santé des Armées (SSA), Vecteurs - Infections Tropicales et Méditerranéennes (VITROME), Marseille, France;

[3] French Armed Forces Center for Epidemiology and Public Health (CESPA), Service de Santé des Armées (SSA), Marseille, France;

[4] Assistance Publique- Hôpitaux de Marseille (AP-HM), Marseille, France;

[5] Aix-Marseille Univ., Institut de Recherche pour le Développement (IRD), Assistance Publique - Hôpitaux de Marseille (AP-HM), Microbes Evolution Phylogeny and Infections (MEPHI), 27 boulevard Jean Moulin, 13005 Marseille, France;

[6] Southeastern Health Regional Observatory (ORS Paca), Marseille, France;

[7] Aix Marseille Univ, School of medicine - La Timone Medical Campus, EA 3279: CEReSS - Health Service Research and Quality of life Center, Marseille, France

* Corresponding author: Stéphanie Gentile, StephanieMarie.GENTILE@ap-hm.fr, Aix Marseille Univ, School of medicine - La Timone Medical Campus, EA 3279: CEReSS - Health Service Research and Quality of life Center, Marseille, France

Abstract

In March 2020, the IHU Méditerranée Infection set up a screening and treatment center for patients with COVID-19, a system that has been ultimately recommended by French public health authorities. The recent publication of the profiles of patients hospitalized in France published by the Directorate for Research, Studies, Evaluation and Statistics gives us the opportunity to measure the impact of this multidisciplinary early management system coupled with screening on mortality at 90 days. Analysis of the data shows that the system established at IHU-MI was associated with lower mortality, taking age and sex into account. Regarding the age-standardized mortality rate, mortality rates were lower than national data regardless of the period of the epidemic. Early management seems to have significantly decreased the mortality rate in the under-60 age group, suggesting the importance of early management, regardless of age. In addition, these patients had pejorative clinical criteria (high NEWS-2 score, ICU visits, oxygen saturation below 95%) requiring hospitalization, and co-morbidities that are now known to be aggravating factors [7]. This reinforces the need to care for all individuals, regardless of age. Early medical care, as part of a system integrating a screening center and a day hospital, may explain the lower mortality rates.

Introduction

In December 2019, a new virus of the coronaviridae family called SARS-CoV-2 emerged in Wuhan, Hubei region, China. It spread rapidly to the rest of the world and was declared a pandemic in March 2020. As of November 16, 2020, there were 1,319,267 patient deaths from COVID-19 [1].

The management of patients with COVID-19 has evolved over time, particularly in France. Indeed, when the first cases appeared in February/March 2020, the only individuals screened were "individuals presenting clinical signs of acute respiratory infection with

documented or subjective fever and who had traveled or stayed in a high-risk exposure zone within 14 days prior to the date of clinical signs, or individuals who have had close contact with a confirmed case of COVID-19 or any person with signs of pneumonia or acute respiratory distress" [2]. Such management did not include any recommendation for mass screening that were already in plance in countries like Iceland or South Korea [3,4]. Indeed, the French government explicitly indicated that screening during the epidemic phase was not necessary [5]. By March 17, the French authorities had implemented a 55-day population lockdown as a health measure. Patients with COVID were instructed to consult emergency services only in case of respiratory difficulties [6]. During the first wave of the new virus, only one treatment was officially recommended to reduce fever in COVID-19 cases: paracetamol [6].

At the same time, the Institut Hospitalo-Universitaire Méditerranée Infection (IHU-MI) based in Marseilles, South-Eastern France offered an alternative management system. The IHU, created in 2011 and funded by the Ministry of Research, is the only research and care facility of this kind dedicated to the fight against infectious diseases in France (https://www.mediterranee-infection.com/). It includes a biology laboratory, 75 hospital beds and research and development teams. In March 2020, the IHU-MI set up a screening and treatment center for patients with COVID-19, a system that has been ultimately recommended by French public health authorities [7]. The IHU offered rapid screening, with results in less than 24 hours, to any individual presenting at the center, as well as outpatient treatment for patients who were positive for SARS-CoV-2. The IHU standardized clinical protocol [8] included: a medical examination with measurement of pulse, blood pressure, respiratory rate and ambient air saturation to evaluate the NEWS-2 score [9], a biological assessment, a low-dose chest CT scan according to age and/or desaturation criteria [10,11]. As regards drug treatment, treatment with hydroxychloroquine-azithromycin in the absence of contraindications with the addition of broad-spectrum antibiotics (ceftriaxone or ertapenem) in patients with a

NEWS-2 score greater than 5 was proposed [8]. When patients had an oxygen saturation below 95% or other clinical signs demonstrating deterioration of the individual's health status, they were then hospitalized at IHU-MI, mostly when they were contagious, to avoid the spread to non-COVID patients and staff. At the peak of the epidemic in April and bed saturation, once they were RT-PCR- negative, patients were transferred to a conventional COVID unit for their remaining care. For outpatients, follow-up was performed at the beginning of the epidemic at D2, D6 and D10 and from 03/2020 onwards only at D10, due to the large number of patients [8].

Patient observation and massive early diagnosis (4,021) made it possible to adapt patient management, which has evolved in line with the knowledge acquired through multidisciplinary collaboration involving cardiologists, radiologists, infectious disease specialists, intensivists and ENT specialists [11-16]. For example, the observation of 'happy hypoxia' has led to the recommendation of ambulatory use of pulse oximeters [13] and the search for high D-dimer anticoagulation levels in patients at risk [14]. This management has been the subject of several publications on clinical and therapeutic results [11,16].

The recent publication of the profiles of patients hospitalized in France published by the DRESS [17] gives us the opportunity to measure the impact of this multidisciplinary early management system coupled with screening on mortality at 90 days.

Materials and methods

Population study

Our study is based on a comparison between patients hospitalized at IHU Méditerranée Infection (IHU-MI) in Marseille, (France) and the inpatient population in France analyzed in the report of the Directorate for Research, Studies, Evaluation and Statistics (Direction de la Recherche, des Études, de l'Evaluation et des Statistiques , DRESS) [17].

The period covers patients hospitalized between March 1 and June 15, 2020. Diagnosis of COVID-19 disease is based on the same criteria for both populations: RT-PCR testing and/or COVID-specific images of COVID disease on chest CT. However, RT-PCR was the essential criterion for the diagnosis of COVID-19 in our Institute.

Criteria for comparison

The comparison between the two hospitalized populations with COVID-19 focuses on age, gender and mortality at 90 days. Hospital mortality was sought for all patients hospitalized at IHU-MI 90 days after admission using the Medical Information Department (DIM) of the Assistance Publique-Hôpitaux de Marseille (AP-HM). This updated death census was carried out on October 21, 2020. However, only deaths that took place in the hospital could be documented.

The clinical characteristics (NEW-2 severity score, oxygen saturation, clinical symptoms on admission and associated comorbidities) of patients hospitalized at IHU-MI were collected but were not compared with the DRESS population, as these data were not available in this dataset.

The percentage of Intensive Care Unit (ICU) visits was observed and compared between the two populations. However, the status of ICU visits was not further analyzed due to the inability to identify ICU and critical care patients in the DRESS study.

Statistical analysis

Categorical variables were presented as n (%) and continuous variables as mean(std) q1-median-q3. We used Fisher's exact test and the Wilcoxon-Mann-Whitney test to compare distributions of categorical and continuous attributes between different categories of patients. One-sided exact binomial tests were performed (when appropriate) to determine if the

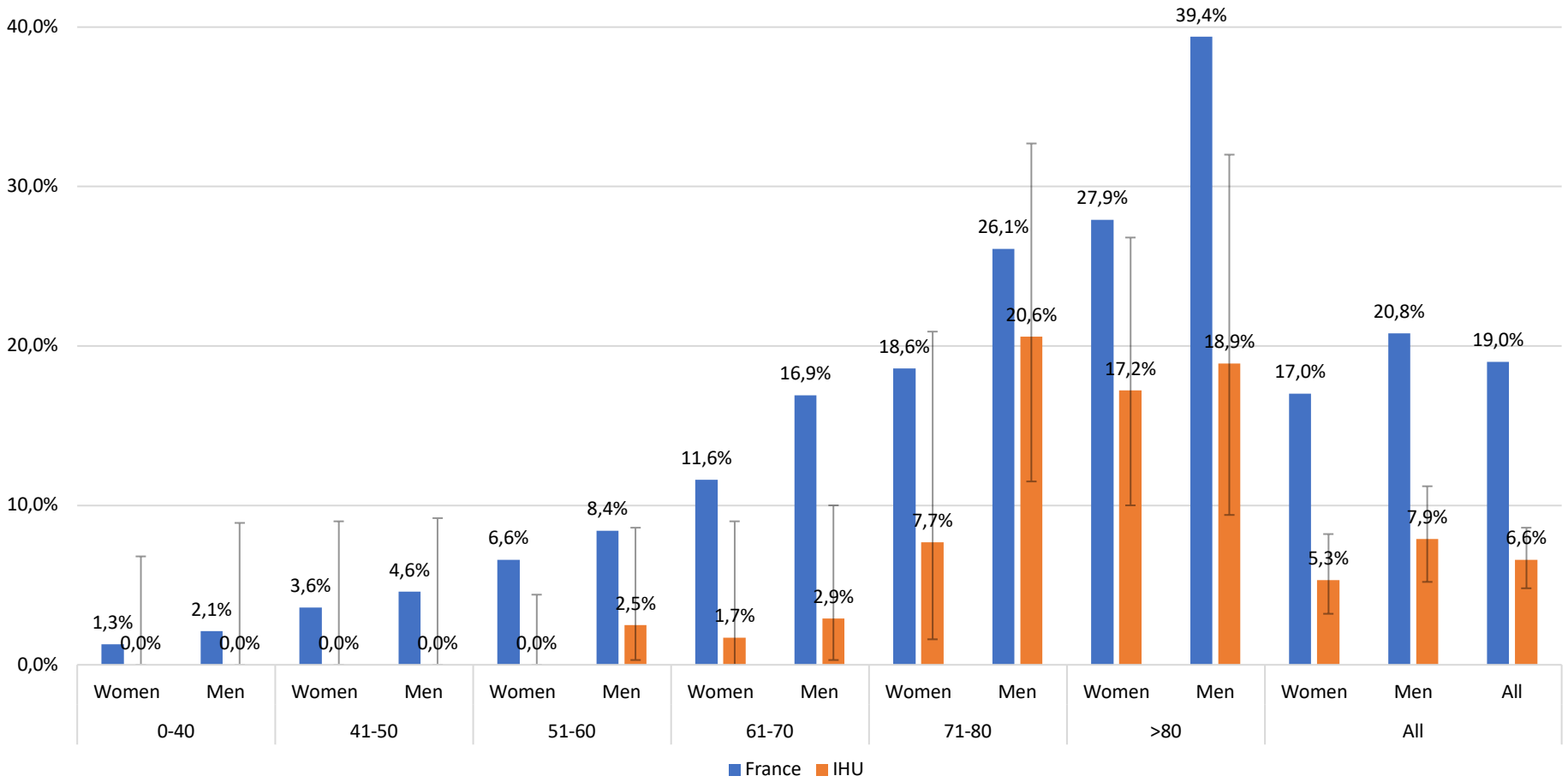
proportions observed in our cohort were significantly lower than national estimates. Two sided 95% confidence intervals were also calculated. To compare death rates at 90 days in our institute with national estimates, we also used direct age standardization. The reference population was all patients hospitalized for COVID-19 between March 1 and June 15 in France (n=91,061). A two-sided p-value of less than 0.05 was considered statistically significant. Analyses were carried out using SAS 9.4 statistical software (SAS Institute, Cary, NC).

Results

Mortality rate 90 days after admission

In France, 17,367 (19%) inpatients died within 90 days of admission compared to 6.6% of patients hospitalized at IHU-MI ($p<0.0001$) (Figure 1). The majority of deaths occurred in the over-80 age group (Figure 1). No deaths occurred in the under-50 age group at MI HUI, while deaths ranged from 1.3% to 2.1% in the 0-40 age group and 3.6 to 4.6% in the 41-50 age group nationally. In older age groups, one sided exact binomial tests indicated that the mortality rates were significantly lower among women aged 71-80 years at IHU-MI (7.7% vs 18.6% - $p=0.0400$) and among patients aged >80 years (18.9% vs 39.4% - $p=0.0011$ and 17.2% vs 27.9% - $p=0.0133$ for men and women, respectively).

Age-standardized mortality rates at HI-MI for the months of March, April and May-June are still lower than those observed in the French national data (Figure 2). The gap between the mortality rates for these two populations narrowed in May-June (7.8% at IHU-MI vs. 12.2% in France). Hospital mortality rates in France decreased over time, from 24.6% in March to 12.2% in May-June. This trend is less marked at the level of our Institute.



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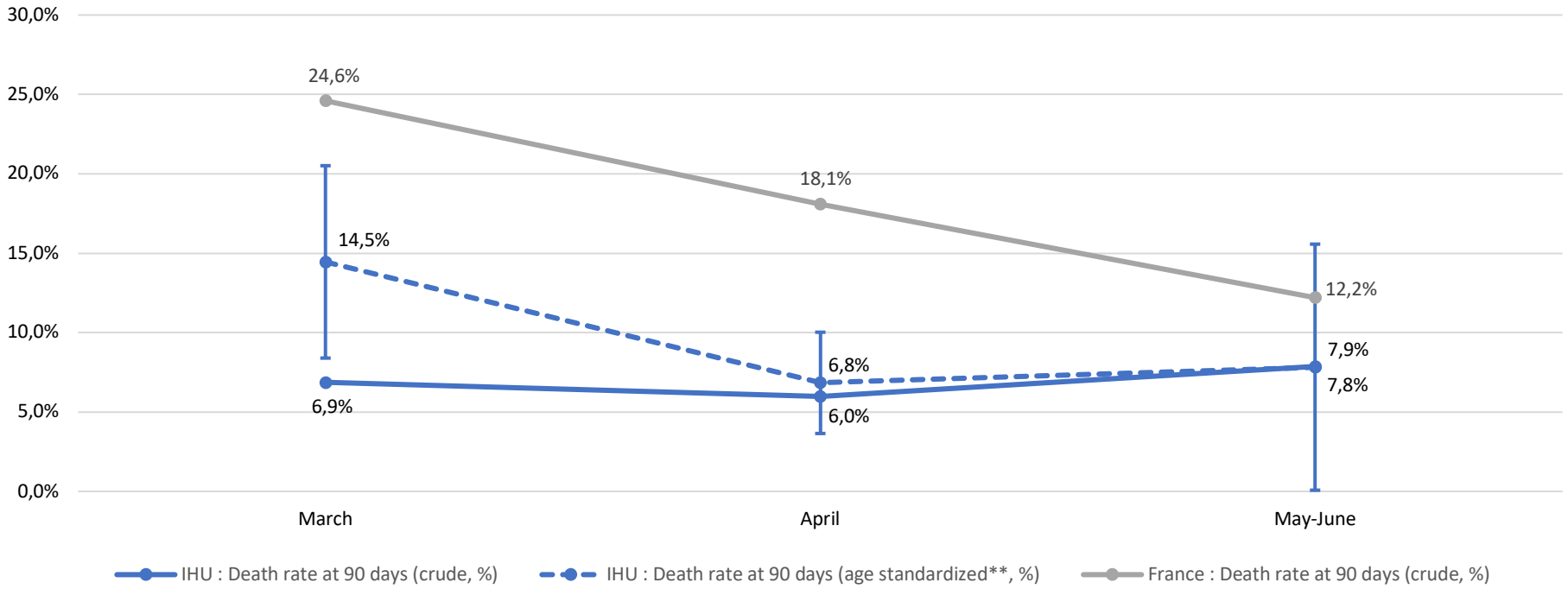
149 *: 95% exact binomial confidence interval

150 Figure 1 – Death rate at 90 days with 95% CI* according to age and gender (%) in France [17] and in our Institute.



*: 95% exact binomial confidence interval

**: Reference population is all patients hospitalized for COVID-19 between March 1 and June 15 in France (n=91 061: 0-40 years 9%; 41-50 years 8%; 51-60 years 14%; 61-70 years 18%; 71-80 years 20% and >80 years 31%).

Figure 2 – Death rate at 90 days with 95% CI* according to the month of admission in France [17] and in our Institute.

158 *Clinical characteristics of patients under 60 years of age hospitalized at IHU-MI*

159 Patients hospitalized at IH-MI were younger. Indeed, the most represented age group
160 was 51-60 years old (23.1% versus 14% in France) and only 19.9% were over 80 years old,
161 versus 31% for France (Table 1).

162 Profile analysis of patients aged 60 (47%) and under showed a pejorative clinical profile,
163 with 13.9% having a NEWS-2 score greater than or equal to 7; 20.0% of subjects aged 60 and
164 under had an oxygen saturation below 95%, and 9.7% had a stay in the ICU (Table 2). Nearly
165 half of the 47% had a comorbidity. The same proportion of individuals with dyspnea is found
166 in those under 60 years and those 60 years and older (36%).

167 **Table 1. Study population characteristics (n=702)**
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	n	%
Sex - Men	344	49.0
Age - Mean(std) Q1-Median-Q3	62.3(18.6)	51-62-77
18-40	101	14.4
41-50	68	9.7
51-60	162	23.1
61-70	129	18.4
71-80	102	14.5
>80	140	19.9
Chronic condition(s)		
Hypertension	273	38.9
Diabetes	146	20.8
Cancer disease	83	11.8
Chronic respiratory diseases	106	15.1
Chronic heart diseases	145	20.7
Obesity	101	14.4
Symptom(s)		
Fever	201	28.6
Cough	361	51.4
Rhinitis	89	12.7
Anosmia	77	11.0
Ageusia	78	11.1
Dyspnea	251	35.8
Thoracic pain	68	9.7
NEWS score - Mean(std) Q1-Median-Q3	4.8(3.3)	2-4-7
0-4	361	51.4
5-6	139	19.8
≥7	202	28.8
O2 Sat (nmiss=1)		
<95	199	28.4
<94	140	20.0
<93	101	14.4
<92	77	11.0
<91	56	8.0
<90	39	5.6
Duration of hospitalization (days) - Mean(std) Q1-Median-Q3	7.5(6.6)	3-6-10
Intensive care unit (ICU)	64	9.1
Duration of ICU (days) - Mean(std) Q1-Median-Q3	14.6(14.2)	5-8-21
Death rate at 90 days	46	6.6

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171 **Table 2. Study population characteristics according to age at admission (n=702)**
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	Patients aged ≤ 60 years (n=331)		Patients aged > 60 years (n=371)		
	n	**%**	**n**	**%**	**P***
Sex - Men	159	48.0	185	49.9	0.6504
Chronic condition(s)					
Hypertension	61	18.4	212	57.1	<0.0001
Diabetes	49	14.8	97	26.2	0.0003
Cancer disease	15	4.5	68	18.3	<0.0001
Chronic respiratory diseases	42	12.7	64	17.3	0.1129
Chronic heart diseases	29	8.8	116	31.3	<0.0001
Obesity	56	16.9	45	12.1	0.0845
At least one chronic condition	155	46.8	290	78.2	<0.0001
Symptom(s)					
Fever	107	32.3	94	25.3	0.0448
Cough	209	63.1	152	41.0	<0.0001
Rhinitis	56	16.9	33	8.9	0.0020
Anosmia	54	16.3	23	6.2	<0.0001
Ageusia	57	17.2	21	5.7	<0.0001
Dyspnea	119	36.0	132	35.6	0.9372
Thoracic pain	53	16.0	15	4.0	<0.0001
Score NEWS-2					
0-4	251	75.8	110	29.7	<0.0001
5-6	34	10.3	105	28.3	
≥7	46	13.9	156	42.1	
O2 Sat (nmiss=1)					
<95	66	20.0	133	38.9	<0.0001
<94	44	13.3	96	25.9	<0.0001
<93	31	9.4	70	18.9	0.0004
<92	22	6.7	55	14.8	0.0006
<91	15	4.6	41	11.1	0.0019
<90	10	3.0	29	7.8	0.0076
Duration of hospitalization (days) - Mean(std) Q1-Median-Q3	6.5(6.1)	3-5-8	8.7(6.9)	4-6-12	<0.0001
Intensive care unit (ICU)	32	9.7	32	8.6	0.6941
Duration of ICU (days) - Mean(std) Q1-Median-Q3	13.0(14.3)	5-6-19	16.2(14.1)	5-12-23	0.3403
Death rate at 90 days	2	0.6	44	11.9	<0.0001

173 *: Fisher exact test / Wilcoxon-Mann-Whitney test

Discussion

Analysis of the data shows that the system established at IHU-MI (systematic screening with rapid reporting of results and comprehensive management of positive results) was associated with lower mortality, taking age and sex into account. Regarding the age-standardized mortality rate, mortality rates were lower than national data regardless of the period of the epidemic. There was also a decrease in the age-standardized mortality rate between March and April, as observed at the national level.

The elderly (over 80 years of age) are the individuals who most frequently die in the context of COVID-19. This was observed in our cohort as well as in France and worldwide. However, the difference in mortality between the IHU population and the DRESS population is greatest in the under-60 age group. Only two deaths (0.6%) in the under-60 group (one 59-year-old and one 60-year-old patient) were noted in our population, compared to 26.6% nationally. Overall, early management seems to have significantly decreased the mortality rate in the under-60 age group, suggesting the importance of early management, regardless of age. In addition, these patients had pejorative clinical criteria (high NEWS-2 score, ICU visits, oxygen saturation below 95%) requiring hospitalization, and co-morbidities that are now known to be aggravating factors [7]. This reinforces the need to care for all individuals, regardless of age. In France, the management of so-called "young" patients has probably been underestimated, given the first available severity criteria. They were not considered to be at risk at the time. Today, recommendations include the existence of co-morbidities as a factor of severity, regardless of age [7].

One of the explanations for these positive results in terms of mortality is undoubtedly access to the exceedingly early care system facilitated by the IHU-MI, which screens and manages COVID-19 patients within the same structure. The implementation of generalized screening open to all; i.e., both symptomatic and asymptomatic individuals, has made it possible

to quickly and easily enter a marked care pathway. Indeed, the time required for treatment of COVID-19 is extremely long and has a strong impact on mortality, similar to oncology. Management is modified according to the disease stage of the patient [8]. The first stage is the appearance of lung lesions and the first clinical signs associated with a high viral load after the incubation period. During this stage, an antiviral was given to the patient if there were no contraindications and was usually combined with the use of a broad-spectrum antibiotic. The second phase corresponds to the persistence of the virus and an immune reaction during which patients, particularly those with risk factors, were particularly monitored. Lymphocytopenia, eosinopenia, elevated troponin or D-dimers greater than 0.5 µg/L were observed during this second phase. Thrombotic complications were monitored. The third stage corresponds to the inflammatory phase, which occurs between day 7 and 10 and is linked to the release of pro-inflammatory cytokines associated with a high risk of transfer to ICU. Severe acute respiratory syndrome (SARS) is the last phase and requires ICU management. It is preferable to manage these patients before this inflammatory phase, when patients who have decompensated are found. In France, many patients who did not have access to a center such as the IHU-MI in the first phase of the epidemic undoubtedly complied with the recommendations of the General Health Directorate and went to the emergency department. Unfortunately, the lockdown and 'happy hypoxia' certainly delayed the management of the patient presenting in a significant inflammatory phase, leading to frequent recourse to the ICU. At IHU-MI, a complete medical examination, including oxygen saturation on ambient air, low-dose thoracic CT scan, and a biological control made it easier to identify patients with no clinical signs of severity but whose lungs were badly damaged. Early medical care, as part of a system integrating a screening center and a day hospital, may explain the lower mortality rates.

The complexity of the health situation; i.e., faced with an unknown disease in the context of a hospital crisis [18] and a non-operational crisis mechanism [19] has disrupted the health

management of this crisis. The IHU-MI model was able to set up an efficient organization; the massive reception (33,503) of patients made it possible to build up a database of observations and research which allowed better understanding of the pathophysiological mechanisms of this disease. The significant difference in mortality rates shows the effectiveness of the IHU-MI model and the need for more in-depth feedback on the different methods of management of SARS-CoV-2 positive patients in order to identify areas for improvement, particularly in the treatment pathway.

Ethic declaration

Data from our cohort were collected retrospectively from the routine care setting using the electronic health recording system of the hospital. Our institutional review board committee (Mediterranée Infection N°: 2020–021) approved this non-interventional retrospective study. According to European General Data Protection Regulation No 2016/679, patients were informed of the potential use of their medical data and that they could refuse the use of their data. The analysis of collected data followed the reference methodology MR-004 registered on N° MR 5010010520 in the AP-HM register.

Consent for publication

Not applicable.

Availability of data and materials

The data from our cohort are not available on the public domain, but anyone interested in using the data for scientific purpose is free to request permission from the corresponding author: Stephanie Gentile (StephanieMarie.GENTILE@ap-hm.fr).

Competing interests

The authors have no competing interests.

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Authors' contributions

Conceived and designed the study: DR, YO and SG. Designed and/or performed experiments: AGG, SC, JCL, MM and PB. Analysed and interpreted data: AGG, YO, DR and SG. Wrote the manuscript: AGG, SC, PPW and SG. All authors read and approved the final manuscript.

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Authors' information

Audrey Giraud-Gatineau[1,2,3,4]; Sébastien Cortaredona[2]; Jean-Christophe Lagier[1,4]; Matthieu Million[1,4]; Philippe Brouqui[1;4]; Yolande Obadia; Patrick Peretti-Watel[2,6]; Didier Raoult; Stéphanie Gentile[7]

IHU Méditerranée Infection, 19-21 boulevard Jean Moulin, 13005 Marseille, France

Audrey Giraud-Gatineau; Jean-Christophe Lagier; Matthieu Million; Philippe Brouqui; Yolande Obadia ; Didier Raoult

Aix Marseille Univ, Institut de Recherche pour le Développement (IRD), Assistance Publique - Hôpitaux de Marseille (AP-HM), Service de Santé des Armées (SSA), Vecteurs - Infections Tropicales et Méditerranéennes (VITROME), Marseille, France

Audrey Giraud-Gatineau ; Sébastien Cortaredona ; Patrick Peretti-Watel

French Armed Forces Center for Epidemiology and Public Health (CESPA), Service de Santé des Armées (SSA), Marseille, France

Audrey Giraud-Gatineau

Assistance Publique- Hôpitaux de Marseille (AP-HM), Marseille, France

Audrey Giraud-Gatineau; Jean-Christophe Lagier[1,4]; Matthieu Million[1,4]; Philippe Brouqui[1;4]; Didier Raoult; Stéphanie Gentile[7]

Aix-Marseille Univ., Institut de Recherche pour le Développement (IRD), Assistance Publique - Hôpitaux de Marseille (AP-HM), Microbes Evolution Phylogeny and Infections (MEPHI), 27 boulevard Jean Moulin, 13005 Marseille, France

Jean-Christophe Lagier ; Matthieu Million ; Philippe Brouqui ; Didier Raoult

Southeastern Health Regional Observatory (ORS Paca), Marseille, France

Patrick Peretti-Watel

Aix Marseille Univ, School of medicine - La Timone Medical Campus, EA 3279: CEReSS - Health Service Research and Quality of life Center, Marseille, France

Stephanie Gentile

Corresponding author

Correspondence to Stephanie Gentile.

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