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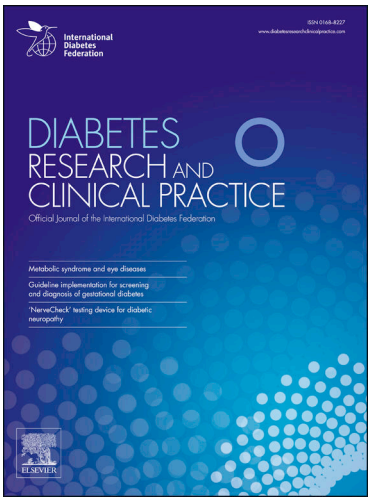

Commentary

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COVID-19 INFECTION IN ITALIAN PEOPLE WITH DIABETES: LESSONS LEARNED FOR OUR FUTURE (an experience to be used).

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As of today March 27, 2020, 86,499 Italian people have been found to be SARS-CoV2 (leading to COVID-19 disease) positive in terms of viral nucleic acid test results on throat swab samples after January 30, when the epidemic conventionally started based on the first documented case in our country, i.e. Mattia (1). The latter, classified as patient 1, was asymptomatic when coming back from Germany to Codogno, his hometown, from where the infection exponentially spread to Bergamo, Lombardy, bordering regions and even further. After that he was diagnosed severe lung disease (which is typically characterized by dyspnea, respiratory rate >30/min, <3% blood oxygen saturation, and/or over 50% lung infiltrates), hospitalized in critical condition (mostly contributed by respiratory failure, septic, and multiple organ dysfunction) and kept in the ICU for 20 days.

By fully recovering and coming back home just a few days ago, he became sort of a symbol and a source of hope for an entire population initially underestimating the seriousness of the epidemic and therefore reacting too slowly in the beginning. From then on, Italians followed the path already paved by the Chinese for two months, consisting of movement restriction and progressive shutdown of all non-essential activities (2-3). This was the beginning of a pandemic, after a century of more or less widespread epidemics all around the world (Figure 1).

For the last few days now, a daily mean 3,000-3,500 infected people incidence has been recorded in Italy, along with a slight decreasing trend in death cases (about 700 or more per day) and a slight increasing trend in healed people (800-850 per day). All this led to a total of 9,134 deaths and 10,950 healings so far. We are aware that not all virus-positive people may be classified as severe cases because some 50% are either totally or partially asymptomatic and just isolated at home (1), as well as, that a public health problem arises from contagion being spread by infected subjects who have not been tested for SARS-CoV2 so far. The hidden transmission phenomenon seems to be especially serious for people suddenly moving from North- to South-Italy in mid-February to reach their families

of origin or more comfortable and warmer country houses, just before stricter infection containment measures were taken. This resulted into several epidemic outbreaks all over Italy, which most likely might have been prevented by earlier more stringent nationwide restriction rules (Figures 2-5).

The news concerning Wuhan province opening to new life again evokes emotions and respect, as well as, stronger commitment to adopted restriction measures, despite the risk to be re-infected by new entries into China being still pending and requiring strict health monitoring procedures to fight the pandemic.

Despite realizing that our individual freedom has been and will be for long sacrificed to essential national needs, we now have to look at the good reverse of the medal represented by government interventions in favor of families, industry and overall economy, by the collaborative attitude shown by almost all political parties, by the large health infra-structure and personnel resources provided by military forces and by the tight adherence of civilians to movement restriction rules.

As a result, 78 hospitals were transformed into COVID-19 oriented structures and the number of ICUs increased from 5343 to 8370 in just a few days mostly, yet not only, in worst affected Northern Italy regions. Tensile structures were also erected close to main emergency units to allow pre-triage activities, isolation and COVID-19 ward admission as needed and several military field hospitals were operationalized in the meanwhile (3).

In addition, all GPs were alerted as a filter between the general population and hospitals to grant active surveillance, telemedicine services were set up to dematerialize prescriptions thus assuring a continuity of innovative drug delivery authorization as needed. Voluntary associations were also encouraged to provide fragile patients with specific drug delivery from temporarily unavailable institutional pharmacies. Finally, several factories started to reconvert in order to produce masks, suits, visors and breathing machines at the national levels to prevent present severe custom clearance problems from threatening health personnel and patient survival. Civil protection calculates needed masks, for instance, to be at least one million per month, i.e. much more than available, and unluckily this increasingly fast-spreading war already involved a number of law enforcement officers and health professionals (40 doctors and even more nurses were killed so far).

Fortunately, all this triggered international solidarity, first of all from China - in terms of expert physicians and tons of medical supplies for our IUCs, followed Cuba, Russia and other countries. Scientific research has also been working hard against COVID-19 since the very beginning so that 20 new drugs and 35 vaccines are under evaluation by EMA (4).

The Italian Drug Agency already triggered several clinical research studies involving remdesivir e tocimizulab and other drugs with originally different therapeutic indications, which - despite great expectations from the public – wait for scientific validation for anti-coronavirus use (5).

COVID-19 predominantly affects male gender and old age with comorbidities, including especially lung disease, arterial hypertension (AH) and diabetes mellitus (DM) (6). Based on Chinese experience, 22% infected people suffered from cerebrovascular diseases, 24 to 12 % from AH and 22 to 12 % from DM, depending on reports. People on angiotensin-converting enzyme (ACE) inhibitors seemed to be at higher risk for clinically severe forms of infection. In fact, based on experimental *in vitro* studies, human pathogenic coronaviruses bind to target cells though angiotensin-converting enzyme 2 (ACE2) - which is expressed by epithelial cells of the lung, intestine, kidney, and vessels (7) - and the expression of ACE2 is increased in patients with DM people - especially those taking either ACE inhibitors or angiotensin II type-1 receptor blockers (ARBs) (7) - and in hypertensive people treated with ACE inhibitors ((8-10), as well as, in patients using thiazolidinediones and ibuprofen. Someone also hypothesized some contribution of an ACE2 polymorphisms linked to diabetes mellitus, stroke, and hypertension to genetic predisposition to SARS-CoV2 infection (11). Such information spread fast thus causing serious alarm and anxiety among users worldwide, who urgently asked their own GPs to change antihypertensive prescriptions straight away. This was

stopped, however, by a prompt reaction from most relevant international scientific societies interested to cardiovascular (CV) diseases, which reassured specialists on the absence of any EBM reasons to adopt such measures only on the basis of an experimentally driven hypothesis and alerted them on the CV risk increase caused by inappropriately discontinuing drugs endowed with well-defined and scientifically proven health benefits (11-13).

Another issue is the possible role of dipeptidyl peptidase IV (DPP-4) in coronavirus infection that seems to be a further emerging issue as regards diabetes. In fact, Corona virus could bind to the human DPP-4 receptor. Kulcsar et al. used type 2 diabetic transgenic mouse models expressing DDP-4 receptor on pulmonary alveolar cells to study the effect of DM on MERS-coronavirus infection severity and, besides showing the latter to be longer-lasting and worse, found a significant association of DM with greater weight loss and pulmonary inflammation, with macrophage infiltrates similar to those seen clinically in the disease (14). Further research is needed of course on that, especially in view of possible therapeutic benefits expected from exploiting DPP4-inhibitors in people with type 2 DM infected by SARS-CoV2.

We should consider, anyway, that both common flu and respiratory tract infections are quite common during cold seasons and, even outside the present COVID-19 emergency, are associated with high morbidity and mortality among people with old age and/or chronic diseases (15-17).

People with DM have been found to be prone to infectious diseases, especially those caused by bacteria and viruses and affecting lower airways (16-19). Mechanisms behind that are unknown at the moment but high glucose levels - which are responsible *per se* for impaired antibacterial neutrophil function – and chronic diabetes-related complications seem to play a relevant role (20). Micro-angiopathic changes might in fact occur in the respiratory tract of DM people, thus hindering gas exchanges and lung *compliance*. Some authors also report on higher susceptibility to lower respiratory tract infections caused by atypical microorganisms and severe penumonia episodes in those with DM (20).

During the last two decades other world-wide respiratory infection outbreaks were observed including influenza A (H1N1) in 2009 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012 (16). In both cases DM was found to be one of host-independent risk factors and was present in people developing fatal complications (20).

This is what we see also in the COVID-19. In a national report of 1,099 selected patients with laboratory-confirmed disease throughout Mainland China during the first 2 months of the current outbreak (10) severe patients were more likely to have DM (16.2% vs. 5.7%) than non-severe patients. This has also been confirmed by data from the current pandemic in Italy, where DM is the second most common disease associated with COVID-19 (Table 2).

AH, ischemic heart disease, heart failure (HF), and end-stage chronic kidney disease were also associated to a higher MERS-CoV-related mortality, which was even further increased by the presence of two or three coexisting above mentioned diseases (21-22). This latter consideration deserves special attention. A higher all-cause hospitalization risk observed in people with DM than in those of comparable age and gender due to the higher prevalence of HF (8%) and respiratory failure (6%) has been reported in clinical records during MERS-CoV (22) and probably is also the case for COVID-19. Available evidence concerning SARS-COV-2 infection features in subjects with DM comes only from data related to infected hospitalized patients, those transferred to the ICUs and death rates. Table 1 summarizes results from main retrospective studies on Wuhan and Hubei / Zhejiang provinces. As already outlined earlier, from available references except for Kui's report (23) the infection seems to mostly affect men. Based on available data, however, there is no possibility to assess whether or not this applies to the DM subpopulation. The percentage range of infected people having DM is 2% to 20% but all studies fail to specify disease type (1 or 2), level of glucose control, home treatment regimen and associated chronic complications. Two of them provide data on ICU

admission rate for people with DM: 7.7% (1 out of 13, $p = 0.16$) in Huang's report (24) and 22.2% (8 out of 36, $p = 0.009$) in Wang's report (25). The study from Xu (26) found 39.4% comorbidity (3.0% being represented by DM) in 33 patients being symptomatic for over 10 days since disease onset. The one from Yang (6), conducted on critically ill patients reported that 21.9% non-surviving patients (7 out of 32) vs 10.0% surviving ones (2 out of 20) had DM. Finally, the Chinese Centre for Disease Control, by analyzing 44,672 confirmed infection cases, reported mortality rate to be 2.3% on the whole, 7.3% in people with DM, 10.5% in those with CV disease and 49% in critically ill patients (28).

Concerning diabetes management, another key issue is: how glycemia is managed during hospitalization for COVID-19?

Unfortunately, it is not surprising that patients suffering COVID-19 with hyperglycemia may have a higher risk and a poorer outcome compared with those with euglycemia (29,30).

Due to the stress by SARS-CoV-2 infection and to the use of glucocorticoids during hospitalization, patients may suffer from a great glycemic excursion, especially for those with DM (31).

We have also to keep in mind that DM management is not so easy to handle in ill people. So, when having to face high glucose levels as expected from the impact of infection *per se* on any unstable metabolic control, it can happen that patients are suddenly switched to insulin, and evidence suggests that insulin treatment might be not safely managed in such situations (32-35).

In fact, when insulin is used at fixed doses or according to the so called "sliding scale" [*], blood glucose is bound to undergo several oscillations around the desirable mean by often getting into the hypoglycemic range and into the hyperglycemic soon after (36,37), which is technically referred as "glycemic variability" (38). Now, hypoglycemia has been shown to potentiate host's innate immune reaction to endotoxins by mobilizing pro-inflammatory monocytes with negative consequences on cardiovascular mortality (39). Hyperglycemia has been known for decades to make people susceptible to infections *per se* by increasing the concentration of several toxic intracellular by-products of the glycolytic pathway (40,41). Moreover, during severe illness glucose overloads and damages cells through the up-regulated expression of glucose transporters on their membranes (42-45). This means that, despite trying to do their best for infected people, Covid-19-units may even unintentionally end up to make the disease more serious because of glycemic variability. During severe influenza virus infection, pulmonary lesions and mortality are driven by massive cytokine (46), and adhesion molecule release (47) by pulmonary endothelial cells which allows the uncontrolled extravasation of leukocytes in the alveolus thus severely damaging respiratory function (47,48). Glucose variability during the hospitalization may increase these phenomena (38), so worsening the prognosis. The above-mentioned considerations already suggested the urgent need for all of us to understand how diabetes increases influenza severity in order to mitigate the burden of future influenza epidemics (49), and even more of present coronavirus pandemic. It deserves attention the fact that large glycemic variability is predictive *per se* of high ICU mortality (50). So, it has already been suggested that the management of glucose variability has to be part of the more comprehensive approach to the management of hyperglycemia today: it seems that this has to be urgently applied in intensive care units (51-52). Even though we understand that in such a critic situation this request should be very hard to implement, we also believe that the best possible action to prevent a worse outcome is also essential in any medical act.

On the other hand, we cannot forget that this situation due to COVID-19 pandemic is very difficult to face for any people with DM. Due to the restrictions applied by many Governments, they have to face hard challenges in getting the needed treatments as well as the required support by the specialists

[*] The term "sliding scale" refers to the progressive change in the pre-meal or nighttime insulin dose, based on pre-defined blood glucose ranges and according to a fixed schedule. Sliding scale insulin regimens approximate daily insulin requirements without any precise evaluation and adaptation to the individual.

or other health care professionals. The seriousness of the epidemic has obviously triggered Associazione Medici Diabetologi (AMD) and Società Italiana Diabetologia (SID), two of the most relevant national scientific societies in the field, which immediately complemented the efforts of Italian Government by strengthening social distancing messages and providing guidelines for their members on how to handle clinical cases during the period (53). They also developed innovative strategies to reduce mortality risk of people with DM from the very beginning by preventing hospitalization as much as possible through a hotline to call for help (54) and enhanced home management. To do so, they made a joint telemedicine effort to have several diabetologists available 7/7 days to take turn for on line advice for drug dosage adaptation needs or any other remotely manageable medical emergencies (55).

In conclusion what can we say we have learned, or better are learning, from this dramatic experience?

As it usually happens, the serious crisis we fell into has to be taken as a real chance for all of us to rethink our own lives, thus turning into moral, social and scientific rebirth for the entire hard-hearted world of today. Specifically, for people living with diabetes, the COVID-19 pandemic is even more complicating their life. Our role is to do all our best to relief them, as much as possible, and, if they happen to be hospitalized, to guarantee them the best therapeutic options, which can be quite different from those to be used in people without diabetes.

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Compliance with ethical standards: Ours was a spontaneous, unconditioned study.

Ethical standard: This study was conducted in conformance with good clinical practice standards. The study was led in accordance with the Declaration of Helsinki 1975, as revised in 2013.

Human and animal rights: This article does not directly use experimental data on humans or animals, but reports data derived from the literature.

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Table 1. Results of main Chinese retrospective studies.

M: males, F: females; n: number; %, percent; CD: chronic diseases; DM: diabetes mellitus; ICU: intensive care unit; CeCVD: cerebro- and cardio-vascular diseases

Studio (ref)	Casi N. (M/F)	Età media (anni)	Malattie Croniche n (%)	Diabete Mellito n (%)	MCeCV n(%)
Wang [25]	138 (**75**/63)	56.0	64 (**46.4%**)	14 (**10.1%**)	20 (**14.5%**)
Kui [23]	137 (61/**76**)	57.0	27 (**19.7%**)	14, (**10.2%**)	10 (**7.3%**)
Chen [27]	99 (**67**/32)	55.5	50 (**51%**)	12 (**12.1%**)	50 (**51%**)
Xu [26]	62 (**35**/27)	41.0	20 (**32%**)	1 (**2%**)	1 (**2%**)
Yang [6]	52 (**35**/17)	59.7	21 (**40%**)	9 (**17%**)	12 (**23.1%**)
Huang [24]	41 (**30**/11)	49.0	13 (**32%**)	8 (**20%**)	6 (**15%**)

Figure 1. Global outbreaks. Worst epidemics in recent history.

* Origin yet to be defined ** Previsional data at the end of March, 2020.

Source: WHO, Johns Hopkins University, modified (last updated, March 26, 2020).

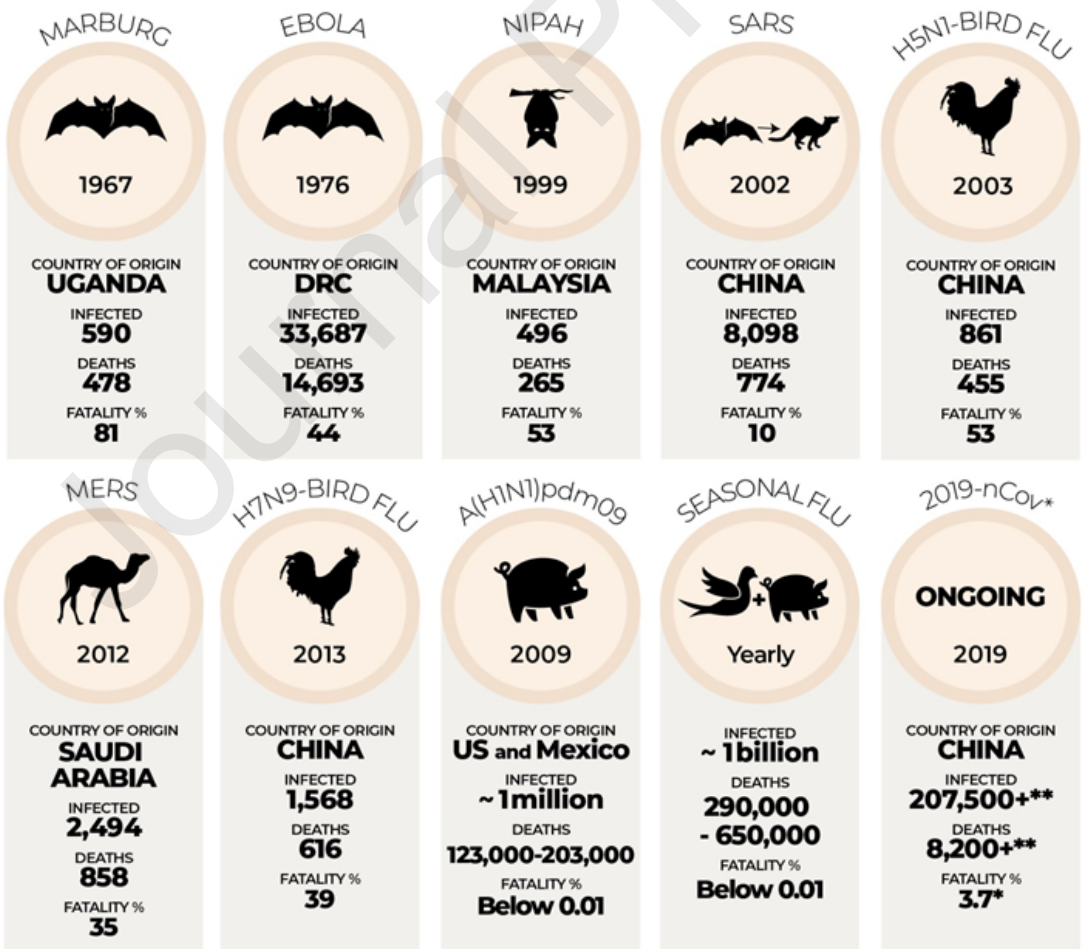


Figure 2. Numbers of COVID-19 in Italy as of March 26, 2020.
(*) positive to virus test; $ hospitalized. *Source: Istituto Superiore di Sanità, modified (last updated, March 26) 2020).* https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_25marzo%20ENG.pdf

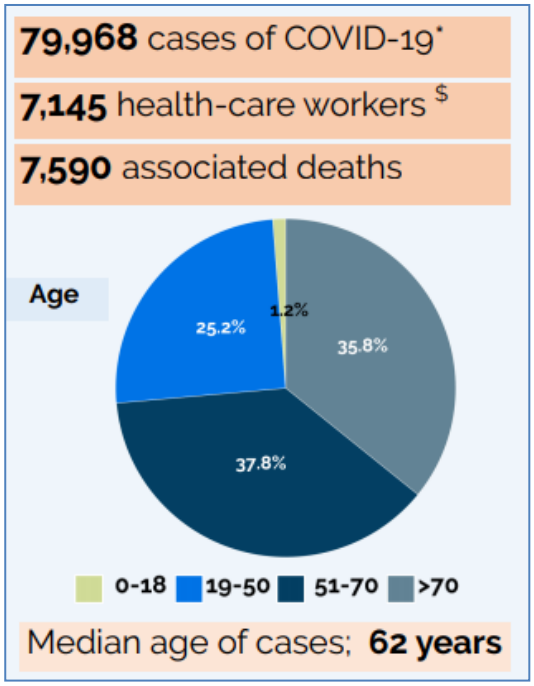
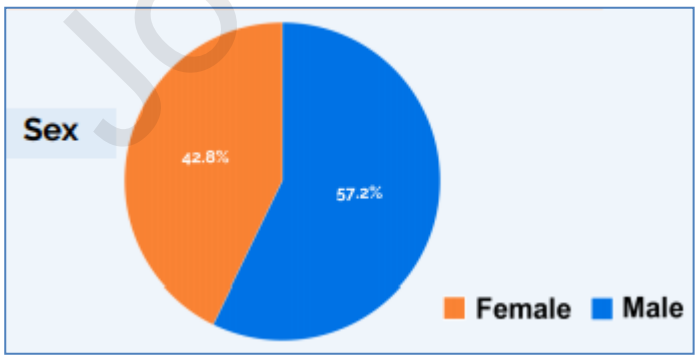


Figure 3. Breakdown by sex (left) and age (right) of Italian COVID-19 patients on March 26, 2020.
Source: Istituto Superiore di Sanità, modified (last updated, March 26).
https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_25marzo%20ENG.pdf



Age (years)	Deaths [n (%)]
0-9	0 (0%)
10-19	0 (0%)
20-29	0 (0%)
30-39	18 (0.2%)
40-49	72 (0.9%)
50-59	275 (3.6%)
60-69	873 (11.5%)
70-79	2660 (35%)
80-89	3010 (39.7%)
>=90	681 (9%)
Not reported	1 (0%)
Total	7590 (100%)

Figure 4. Trend of the COVID-19 epidemic in Italy. *Source: Italia Tutto Bene, modified (last updated, March 26,2020).* https://www.italiatuttobene.it/ (accessed on March 26, 2020)

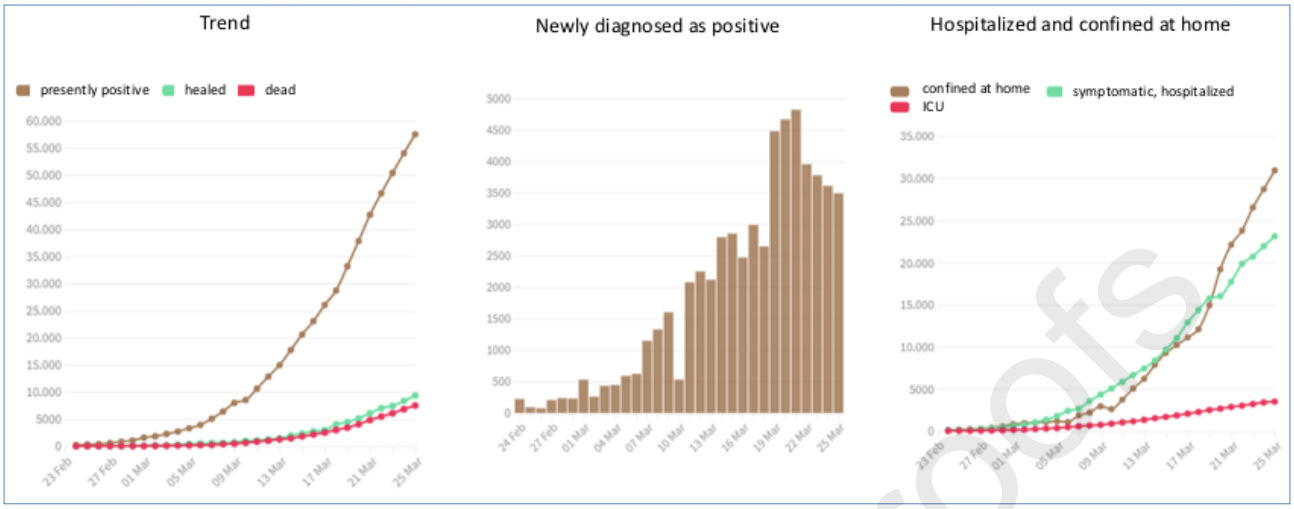


Table 2. Comorbidities of subjects affected by Coronavirus-19 in Italy. *Source: Istituto Superiore di Sanità, modified (last updated, March 26).*
https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_25marzo%20ENG.pdf

Type of comorbidity	(%)	Number and % of comorbidities	
ischemic heart disease	30.1	0	1.2
atrial fibrillation	22.0	1	23.5
stroke	11.2	2	26.6
arterial hypertension	73.8	3 or more	48.6
diabetes mellitus	33.9		
dementia	11.9		
chronic obstructive pulmonary disease	13.7		
active cancer in the past 5 years	19.5		
chronic liver disease	3.7		
chronic renal failure	20.2		

Figure 5. Total number of COVID-19 cases diagnosed by the Italian Regional Reference Laboratories on March 26, 2020. Source: Istituto Superiore di Sanità. https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_25marzo%20ENG.pdf