Describing the epidemic trends of COVID-19 in the area covered by Agency for Health Protection of the Metropolitan Area of Milan

Descrizione dell'andamento dell'epidemia di COVID-19 nell'ATS di Milano

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ABSTRACT

OBJECTIVES: to describe the epidemic trends of COVID-19 over time and by area in the territory covered by Milan's Agency for Health Protection (ATS-MI) from February to May 2020.
DESIGN: descriptive study of COVID-19 cases.
SETTING AND PARTICIPANTS: a new information system was developed to record COVID-19 cases with positive nasopharyngeal swab. Patients resident in the area covered by ATS-MI with symptom onset between February and May 2020 were selected. Different epidemic periods were considered based on the timeline of the various regional and national containment measures.
MAIN OUTCOME MEASURES: case fatality ratios, incidence rates, and reproduction number by epidemic period and sub-area of ATS-MI.
RESULTS: a total of 27,017 swab-positive COVID-19 cases were included. Mean age was 65 years and males were 45%. Incidence in the ATS-MI area was 776 per 100,000 population. The number of deaths was 4,660, the crude case fatality ratio was 17.3%, higher in males (21.2%) than in females (14.0%). The estimated reproduction number registered its peak (3.0) in the early stages of the epidemic and subsequently decreased. Territorial differences were observed in the epidemic spread, with a higher incidence in the Lodi area.
CONCLUSIONS: estimated incidence and case fatality ratios were higher than national estimates for Italy. Each ATS-MI area had different epidemic spread patterns.

Keywords: COVID-19, case fatality ratio, incidence, comorbidities, information systems

RIASSUNTO

OBIETTIVI: descrivere l'andamento temporale e spaziale dell'epidemia di COVID-19 nel territorio dell'ATS di Milano nel periodo febbraio-maggio 2020.
DISEGNO: studio descrittivo dei casi di COVID-19
SETTING E PARTECIPANTI: un sistema informativo dedicato ha permesso di registrare i casi di COVID-19, con positività del tampone nasofaringeo residenti nel territorio dell'ATS-MI. Sono inclusi i casi con data di insorgenza dei sintomi compresa tra febbraio e maggio 2020. I dati sono stati analizzati in base agli intervalli di tempo caratterizzati dalle diverse misure di contenimento dell'epidemia intraprese a livello regionale e nazionale.
PRINCIPALI MISURE DI OUTCOME: percentuale di letalità tra i casi con tampone positivo, tasso di incidenza e indice di riproduzione del COVID-19 nei diversi periodi epidemici e suddivisioni territoriali dell'ATS-MI.
RISULTATI: sono stati registrati 27.017 casi COVID-19 positivi al tampone. I maschi sono il 45% e l'età media è di 65 anni. L'incidenza sul territorio dell'ATS-MI è stata di 776 per 100.000 abitanti. I deceduti sono 4.660, il tasso grezzo di letalità del 17,3%, superiore nei maschi (21,2%) rispetto alle femmine (14,0%). Il numero di riproduzione dei casi nel tempo è massimo nei periodi iniziali dell'epidemia (3,0) e poi decresce successivamente. Si rileva la presenza di diverse intensità di contagio nel territorio dell'ATS-MI con il territorio del Lodigiano maggiormente colpito rispetto al resto dell'ATS-MI.
CONCLUSIONI: le stime di incidenza e mortalità sono superiori a quanto riportato per il territorio italiano. Sul territorio dell'ATS-MI vengono evidenziati diversi pattern di andamento dell'epidemia.

Parole chiave: COVID-19, mortalità, incidenza, comorbidità, sistemi informativi

WHAT IS ALREADY KNOWN

- **Lombardy was particularly hard hit by the COVID-19 epidemic, the Italian case fatality ratio is one of the highest in the world.**
- **Fatality is higher in males and in older patients with comorbidities.**
- **Containment measures can help control the spread of COVID-19.**

WHAT THIS STUDY ADDS

- **The study made it possible to trace the spread of COVID-19 in Milan's ATS as a whole and in the local districts, each of which had its own particular epidemic curve.**
- **Throughout the area covered by Milan's ATS, control of the epidemic, in terms of reduction of the reproduction number below 1, was reached two weeks after the start of the national lockdown.**

INTRODUCTION

Lombardy was the first region in Italy to diagnose a case of person-to-person transmission of COVID-19, on 20 February 2020 in Codogno (province of Lodi), and was one of the hardest hit Italian regions.[1]

When the first case was diagnosed, regional and local infectious disease containment protocols were activated, along with specific WHO protocols for pandemic management,[2] which call for identification within the region of all confirmed cases of disease and their close or occasional contacts by means of a phone interview conducted by specialized personnel.

Within Lombardy's health system, the Agency for Health Protection of Milan, ATS-MI, is in charge of the provinces of Milan and Lodi, serving about 3.5 million people.[3] The area covered by ATS-MI is subdivided into local health units (ASST) (figure 1), which are responsible for providing health and social services in the area they cover.

Within four days, spreading of the infection in the province of Lodi required the creation of an area of isolation ("red zone"), along with travel restrictions, limitation of activities involving crowds, and promotion of remote work throughout the region. The epidemic outbreak resulted in national lockdown measures being issued on 8 March,[4] imposing the shuttering of all recreational activities and non-essential business, schools, and universities, and a travel ban between Italian regions. Starting on 21 March,[4] stricter measures were introduced nationally and all productive activities that were not deemed essential were shut down throughout Italy. Starting on 4 May,[4] a gradual lifting of restrictions began, although, until 4 June, rules on social distancing, mandatory wearing of face masks, and travel limitations in Italy remained in place, and schools and childcare services remained closed.

This paper describes the impact of the epidemic in the areas of ATS-MI with respect to a) the characteristics of the microbiologically confirmed COVID-19 cases and the mortality outcome; b) the spatial and time trends, with respect to each epidemic period as defined by the containment measures, and trends by ATS-MI area.

MATERIALS AND METHODS

ATS-MI, upon detection of the first case diagnosed with a positive swab, implemented specific monitoring of the spread of COVID-19 with the creation of a web-based information system, ***Milano COV***, which recorded microbiologically confirmed cases detected through the SARS-CoV-2 positive test (PT) data flow transmitted daily by laboratories. ***Milano COV*** can interact with the current ATS-MI flows, to find the personal information (gender, age) and residential information (ASST and town of residence, nursing home) of patients.

Thanks to direct access by the over 200-strong staff of the Department of Prevention, ***Milano COV*** made it possible to manage telephone interviews, showing operators the names of people to contact, providing their contact information, and allowing for web-based recording of the epidemiological phone interviews. During interviews, for each diagnosed patient the date of onset of the first symptoms and the date on which the test was performed were recorded. Registration of patient interview data made it possible to trace the spread of the virus even in the period preceding the first officially diagnosed case and attribute clinical onset dates prior to 20 February for cases confirmed by PT at a later date.

IDENTIFICATION OF CASES

As described above, ***Milano COV*** contains case data, i.e., data of patients with a positive test. The case cohort is made up of cases of patients and residents in the ATS-MI area with RT-PCR positive test for SARS-COV-2 present in ***Milano COV*** as of 31 May 2020. All analyses reported below were carried out on this cohort of PT patients; the date of symptom onset reported in the epidemiological interview was used as date of diagnosis. Through record linkage with Lombardy's regional chronic disease database,[5] we traced the main patterns of comorbidities.

DEFINITION OF THE EPIDEMIC PERIODS AND RELEVANT CONTAINMENT MEASURES

The epidemic phase of COVID-19 in Lombardy was divided into five periods, based on the measures taken to contain the epidemic. The pre-epidemic period (P0), in which patients who had symptom onset before 20 February 2020 were included. The first period (P1) from 20 February (first case) to 23 February, when the *red zone* around Codogno (province of Lodi) was established, the second period (P2) from 24 February to 8 March, when, in addition to Codogno's red zone, containment measures were in place throughout the region of Lombardy. The third period (P3) from 9 March to 3 May, corresponding to the national lockdown, and a last period (P4) from 4 to 30 May 2020, in which there was a progressive lifting of the shutdown measures. The lockdown measures in Lombardy did not significantly change after 21 March, so there was no further subdivision of the study period.

STATISTICAL ANALYSIS

CASE DESCRIPTION

The outbreak is described using frequencies and percentages both overall and by epidemic period. Data taken into consideration were demographic variables (gender and age class), patients' local health unit (ASST) (figure 1), the presence of pre-existing chronic diseases, with particular focus on some of the comorbidities associated with a previously reported greater risk of adverse events in patients with COVID-19 (diabetes, high blood pressure, cardiovascular disease, cancer, dialysis and kidney failure).[6,7] The case fatality ratio (CFR) was calculated on the overall number of deaths among PT patients. Normal approximation to a bi-

	AREA Km²	POPULATION No.
ASST Lodi	790	237,000
ASST Melegnano	570	364,000
ASST Milano	180	1,380,000
ASST Nord-Milano	43	270,000
ASST Ovest-Milano	559	465,000
ASST Rhodense	200	485,000

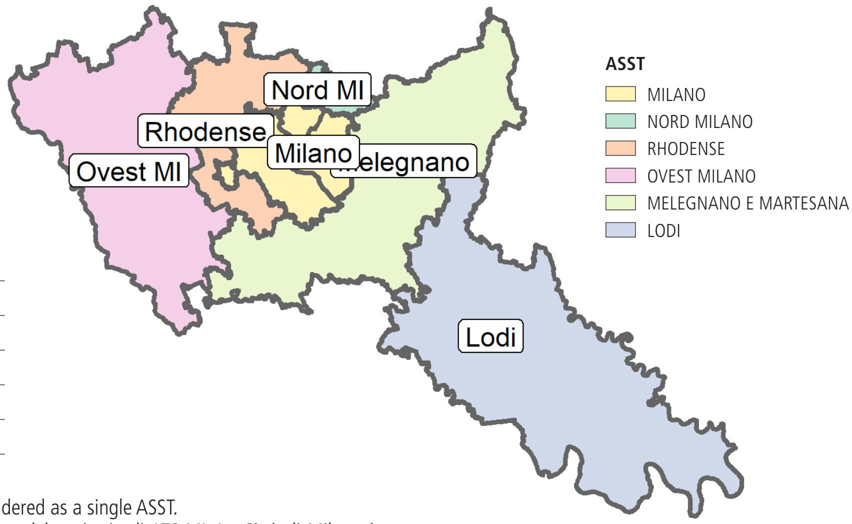


Figure 1. ASST districts within ATS-MI. Milan was considered as a single ASST.
Figura 1. Distribuzione territoriale delle ASST all'interno del territorio di ATS-MI. La Città di Milano è stata considerata in un'unica ASST.

nomial distribution was used to calculate the confidence interval (CI). The different distribution of proportions between binary and categorical variables was assessed using a chi-square test, or ANOVA when appropriate. The association between probability of death and age, gender, ASST of residence, epidemic period, and the presence of pre-existing chronic diseases was investigated with a multivariate logistic regression model, the results of which are reported in terms of odds ratio (OR) and 95% confidence intervals.

EPIDEMIC TRENDS BY AREA AND OVER TIME

Overall and for each ASST, incidence curves of the number of daily cases were obtained, displayed using natural cubic splines with 10 knots[8] (Supplementary Material, Statistical methods for splines). The reproduction number (R_t) was calculated as suggested by Cori[9] (Supplementary Material, Statistical methods for the calculation of the reproduction number).

Both for the incidence curves and for R_t, symptoms with onset after 10 February and until 30 May 2020 were considered, so as to only use consolidated data.

Beginning on 20 February, for each period and each ASST, the daily ratio of COVID-19 cases was calculated, i.e., the cases per day-person (CDP) per 100,000, defined as the number of cases of each period divided by the period number of days (4, 14, 56, 27, respectively for each identified period, P1-P4) per 100,000 people (pop.), using as reference the Istat population of each town as of 01.01.2020.[3]

The same rates were calculated and graphically displayed using a map for each town, with the exception of the municipality of Milan, for which each postal code was considered.

RESULTS

DESCRIPTION OF PCR-CONFIRMED POSITIVE CASES

In ***Milano COV***, 27,362 cases notified as PT were recorded, 345 (1.3%) of these were excluded from subsequent analysis because the symptom onset date, ascertained through epidemiological interview, was missing. The median time interval between symptom onset and testing date was 3 days (I-III quantile 0-10 days). The time interval between symptom onset and testing was higher in the P0 period: 15 days (I-III quantile 8-31), compared to subsequent phases: P1: 8 (I-III 2-13); P2: 7 (I-III 3-12); P3 3(I-III 0-9); P4: 2 (I-III 0;3).

The percentage of hospitalized patients was 39% overall and varied depending on the epidemic period in which symptoms developed. The percentage of hospitalized patients was 69% for individuals with symptom onset in the initial periods (P0 and P1), 64% for cases with onset of symptoms during lock down (P3), while for subjects who developed symptoms in the final stage of the epidemic (P4) the percentage of hospitalized patients was 37%.

Out of the 27,017 cases described, 12,071 (44.7%) were men and 14,496 (55.3%) were women (Table 1). The distribution by gender was different in the four stages of the epidemic: men were preponderant in the first stages, P1 and P2 (respectively, 59.6% and 59.1%), while in later stages the share of women increased (in P3 and P4 they were 57.1% and 67.9%, respectively). The mean age varied across the stages of the epidemic: it was lower in P2 (63 years) and higher in the initial period of the epidemic (66 years). The percentage of cases who were 80+ years of age was greater in P3 and P4 (34.2% and 37.7%, respectively). Patients with at least one pre-existing chronic disease were 55.8%. Presence of pre-existing chronic diseases varied across the four stages of the epidemic and decreased over time (from 66.9% in P0 to 47.2% in P4, p-value for trend <0.001, data not shown). The most frequent comorbidity was high blood pressure (36.8% of cases), followed by heart disease (22.2%). Subjects with PT presented a slightly higher comorbidity incidence compared to the general over-40 population of ATS-MI (Supplementary Table S1).

The deceased (Table 1) were 4,660, with a 17.3% CFR (95%CI 16.8-17.7) overall and a 21.2% CFR (95%CI 20.4-22.0) among men (vs. 14.0% – 95%CI 13.5-14.6 – in women, χ^2 p<0.001). For 113 cases, the testing date was the same as the date of death. The mean age at death was 80.5 years, higher for women than for men (84.1 vs 77.6; t-test p<0.001). CFR in the 60 to 79 year age class

CHARACTERISTICS	P0	P1	P2	P3	P4	TOTAL	DECEASED#	OR (95%CI)*
	SYMPTOM ONSET PRIOR TO 20 FEB 2020	SYMPTOM ONSET 20-23 FEB 2020	SYMPTOM ONSET 24 FEB-8 MAR 2020	SYMPTOM ONSET 9 MAR-3 MAY 2020	SYMPTOM ONSET 4-30 MAY 2020			
	No. 290	No. 374	No. 3,762	No. 20,370)	No. 2,221	No. 27,017	No. 4,660	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
GENDER								
Men	168 (57.9)	223 (59.6)	2,223 (59.1)	8,744 (42.9)	713 (32.1)	12,071 (44.7)	2,562 (21.2)	2.03 (1.89-2.91)
Women	122 (42.1)	151 (40.4)	1,539 (40.9)	11,626 (57.1)	1,508 (67.9)	14,946 (55.3)	2,098 (14.0)	ref
AGE CLASS								
<20	-	9 (2.4)	40 (1.1)	214 (1.1)	79 (3.6)	342 (1.3)	1 (0.3)	0.14 (0.02-0.99)
20-39	26 (9.0)	27 (7.2)	340 (9.0)	2,258 (11.1)	356 (16.0)	3,007 (11.1)	10 (0.3)	0.15 (0.08-0.90)
40-59	67 (23.1)	109 (29.1)	1,180 (31.4)	5,738 (28.2)	563 (25.3)	7,657 (28.3)	190 (2.5)	ref
60-79	136 (46.9)	154 (41.2)	1,466 (39.0)	5,199 (25.5)	385 (17.3)	7,340 (27.2)	1,647 (22.4)	8.31 (7.09-9.73)
80+	61 (21.0)	75 (20.1)	736 (19.6)	6,961 (34.2)	838 (37.7)	8,671 (32.1)	2,812 (32.4)	19.40 (16.58-22.75)
ASST								
Lodi	179 (61.7)	255 (68.2)	1,049 (27.9)	1,840 (9.0)	298 (13.4)	3,621 (13.4)	692 (19.1)	1.05 (0.94-1.18)
Melegnano	27 (9.3)	27 (7.2)	754 (20.0)	3,642 (17.9)	356 (16.0)	4,806 (17.8)	823 (17.1)	0.99 (0.89-1.09)
Milano	47 (16.2)	45 (12.0)	956 (25.4)	7,893 (38.7)	878 (39.5)	9,819 (36.3)	1,740 (17.7)	ref
Nord Milano	13 (4.5)	16 (4.3)	325 (8.6)	1,828 (9.0)	184 (8.3)	2,366 (8.8)	406 (17.2)	0.95 (0.83-1.08)
Ovest Milano	16 (5.5)	16 (4.3)	383 (10.2)	2,386 (11.7)	250 (11.3)	3,051 (11.3)	457 (15.0)	0.86 (0.76-0.97)
Rhodense	8 (2.8)	15 (4.0)	295 (7.8)	2,781 (13.7)	255 (11.5)	3,354 (12.4)	542 (16.2)	0.90 (0.80-1.03)
COMORBIDITY								
Cancer	28 (9.7)	26 (7.0)	236 (6.3)	1,018 (5.0)	89 (4.0)	1,397 (5.2)	453 (32.4)	1.52 (1.33-1.73)
Hypertension	140 (48.3)	165 (44.1)	1,515 (40.3)	7,483 (36.7)	640 (28.8)	9,943 (36.8)	2,819 (28.4)	1.21 (1.11-1.31)
High cholesterol	54 (18.6)	64 (17.1)	487 (12.9)	1,957 (9.6)	141 (6.3)	2,703 (10.0)	878 (32.5)	1.13 (1.02-1.25)
Chronic kidney fail.	6 (2.1)	16 (4.3)	95 (2.5)	552 (2.7)	49 (2.2)	718 (2.7)	274 (38.2)	1.34 (1.13-1.59)
Dialysis	2 (0.7)	1 (0.3)	24 (0.6)	136 (0.7)	7 (0.3)	170 (0.6)	64 (37.6)	1.88 (1.33-2.67)
Diabetes	41 (14.1)	43 (11.5)	562 (14.9)	2,624 (12.9)	201 (9.0)	3,471 (12.8)	1,095 (31.5)	1.30 (1.90-1.43)
Heart disease	81 (27.9)	103 (27.5)	838 (22.3)	4,556 (22.4)	409 (18.4)	5,987 (22.2)	1,976 (33)	1.20 (1.10-1.30)
Other comorbidity	103 (35.5)	127 (34.0)	1,236 (32.9)	6,438 (31.6)	618 (27.8)	8,522 (31.5)	2,174 (25.5)	1.12 (1.03-1.21)

* Adjusted per epidemic period: OR P0 vs. P3: 1.26 (95%CI 0.94-1.66); P1 vs. P3: 0.93 (0.69-1.26); P2 vs. P3: 1.48 (1.34-1.64); P4 vs. P3: 0.13 (0.10-0.17); P3 is used as reference since it is the period with the greatest number of patients. / *Aggiustato per periodo di pandemia: OR P0 vs P3: 1,26 (IC95% 0,94-1,66); P1 vs P3 0,93 (0,69-1,26); P2 vs P3 1 ,48 (1 ,34-1 ,64); P4 vs P3 0,13 (0,10-0 ,17), P3 come riferimento in quanto periodo con più pazienti.*

Percentage of deceased / *Percentuale di deceduti*

Table 1. Distribution of COVID-19 patients by gender, age class, comorbidity, and deaths for TP COVID-19 patients by age, gender, comorbidity and epidemic phase. Symptom onset date was defined by epidemiological investigation.
Tabella 1. Distribuzione per età, genere, condizioni pre-esistenti e decesso dei pazienti tampone positivo per fase epidemica. La data di inizio sintomi riportata si riferisce alla data determinata mediante l'indagine epidemiologica.

was 22.4% (95%CI 21.5-23.3), while in the over 80 age class it was 32.4% (95%CI 31.4-33.4). The crude case fatality ratio was different across the ATS areas: it was higher in the province of Lodi (CFR 19.1%; 95%CI 17.8-20.3), and lower in ASST Ovest Milanese (Milan-West) (CFR: 15.0%; 95%CI 13.7-16.2).

In the model analysing the individual types of comorbidity, mortality was higher for all examined diseases compared to the reference group (subjects with no comorbidities); in particular, dialysis patients had an almost twofold risk (OR: 1.88; 95%CI 1.33-2.67) and cancer patients who underwent treatment in 2019 had a risk that was more than one and a half times higher (OR: 1.52; 95%CI 1.33-1.73). As expected, people over 60 years of age had an OR of death which is distinctly higher than people between 40 and 59 years of age; the risk rose up to 20 times higher in patients over 80 (OR 60-79 years old vs. 40-59 years old: 8.31; 95%CI 7.09-9.73; OR 80+ years vs. 40-59 years: 19.40 95%CI 16.58-22.75).

EPIDEMIC TREND OVER TIME AND BY AREA

Figure 2A shows the overall epidemic curve. Distribution is asymmetrical, with a very rapid initial surge followed by a slow decline, with onset of half of cases by 25 March and maximum daily number of cases recorded on 10 March.

The estimated reproduction number R_t (Figure 2B) shows a variable trend in the first stages of the epidemic, reaching a maximum estimated value of 3.0 (95%CI 2.6-3.3) on 20 February. In the following epidemic stages, the value of R_t tended to decrease, until it was stably under 1 starting on 23 March. The minimum estimated value before the lockdown was lifted was reached on 1 May (R_t 0.73; 95%CI 0.69-0.78). In P4, R_t was stably below one, fluctuating around 0.70: with a minimum of 0.66 (95%CI 0.61-0.70) on 7 May and a maximum of 0.78% (95%CI 0.70-0.85) on 27 May. Figure 3 shows the distribution by area of the spread of the COVID-19 epidemic. The number of cases per 100,000 throughout the ATS-MI area as of 30 May 2020 was 776. The ratio varied by ASST: Lodi had the highest ratio (1,523 per 100,000), while Milan West

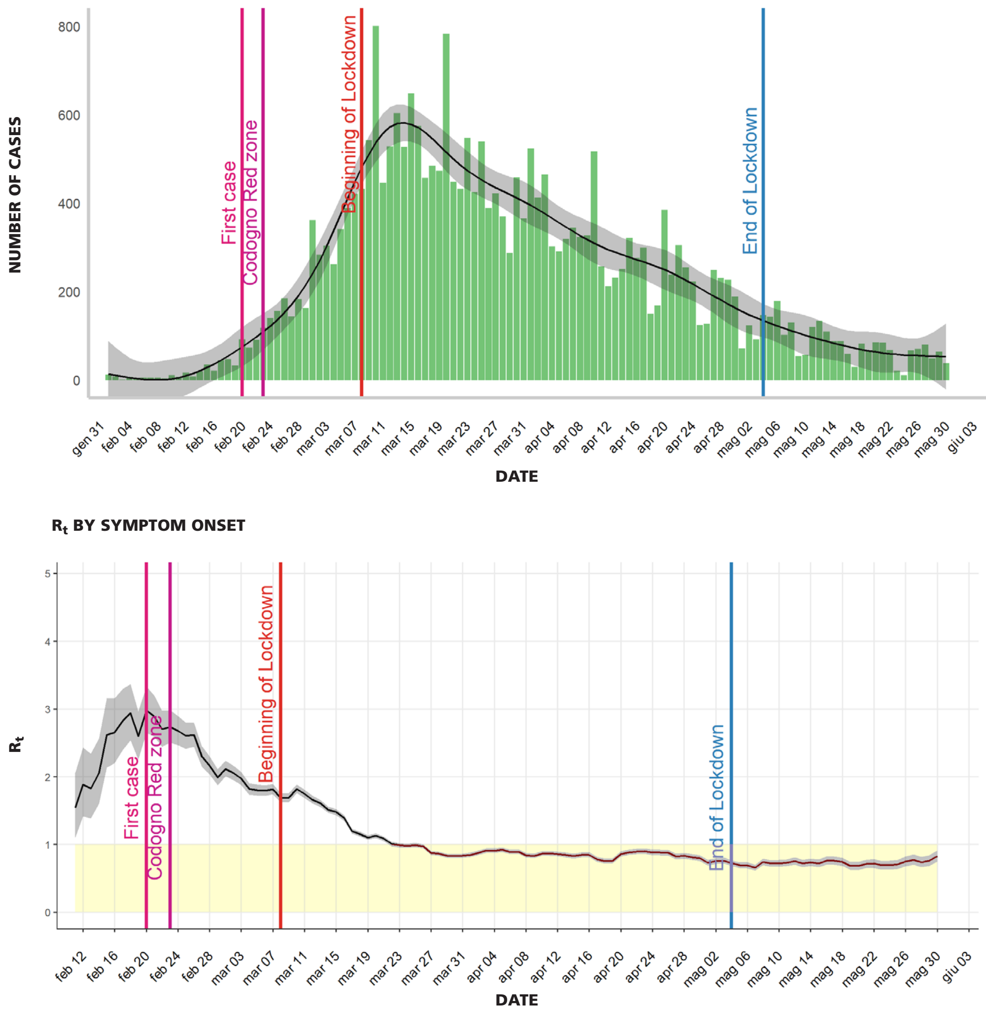


Figure 2. **A.** The epidemic curve of COVID-19 in Milan's ATS between 1st February and 30rd May 2020. Vertical lines indicate the beginning of each period (first case, Codogno "red zone", beginning of lockdown, end of lockdown). The black line is the smoothing with 95% confidence intervals using cubic function. **B.** Reproduction number in ATS-MI.

Figura 2. **A.** Curva epidemica del COVID-19 nell'ATS-MI tra il primo febbraio e il 30 maggio 2020, le linee verticali riportano le date di inizio dei diversi periodi di contenimento dell'epidemia, la linea nera riporta la curva smussata ottenuta mediante spline cubiche con dieci nodi e i relativi intervalli di confidenza al 95%. **B.** Curva dell'indice di riproduzione (Rt) per l'ATS di Milano.

had the lowest (656 per 100,000). In table 2 (and figure 4) we can observe the trends of the number of CDPx100,000 throughout the ATS-MI area in the four epidemic periods. In P1, the disease can be observed to be present in the area south of Lodi (26.8 CDP×100,000; 95%CI 23.6-30.2) with a south to north gradient. In P2, besides the area of the province of Lodi (31.5 CDP×100,000; 95%CI 29.6-33.5), infections spread in other areas (ASST Melegnano: 8.4 95%CI 7.8-9.0 and Milan North: 8.6 CDP×100,000; 95%CI 7.7-9.6). In the third period (P3) the infection spread across the entire ATS area; a high number of daily cases can still be observed in the province of Lodi, though on the decline (13.8 CDP×100,000; 95%CI 13.2-14.5) and comparable to other areas, which had values ranging from the highest value for the Milan North ASST (12.1 CDP×100,000; 95%CI 11.5-12.6) and the lowest for the Milan West ASST (9.2 CDP×100,000; 95%CI 8.8-9.5). After 4 May (P4), a slowdown of the epidemic can be observed, with a daily incidence of cases that remains slightly higher in the province of Lodi than in the other ASSTs.

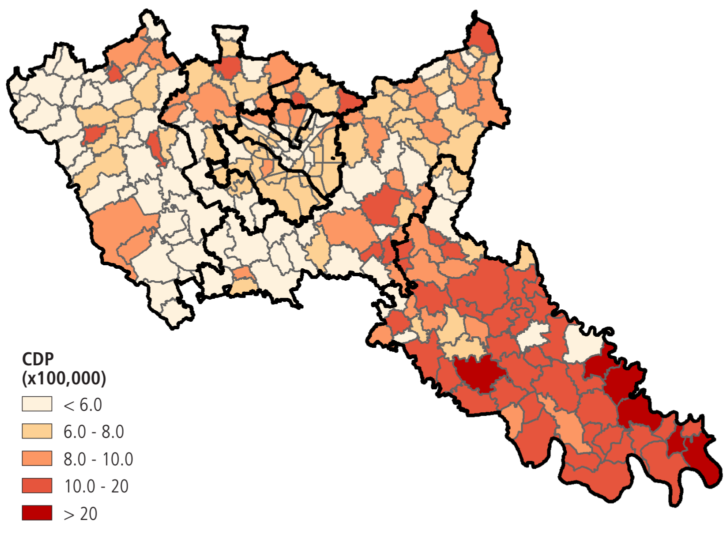


Figure 3. Daily rate of cases (CDP) of COVID-19 per 100,000 in Milan's ATS between February and May 2020.

Figura 3. Casi giorno-persona (CDP) di COVID-19 nel territorio dell'ATS di Milano per 100.000 nel periodo tra il 20 febbraio e il 30 maggio 2020 (P1-P4).

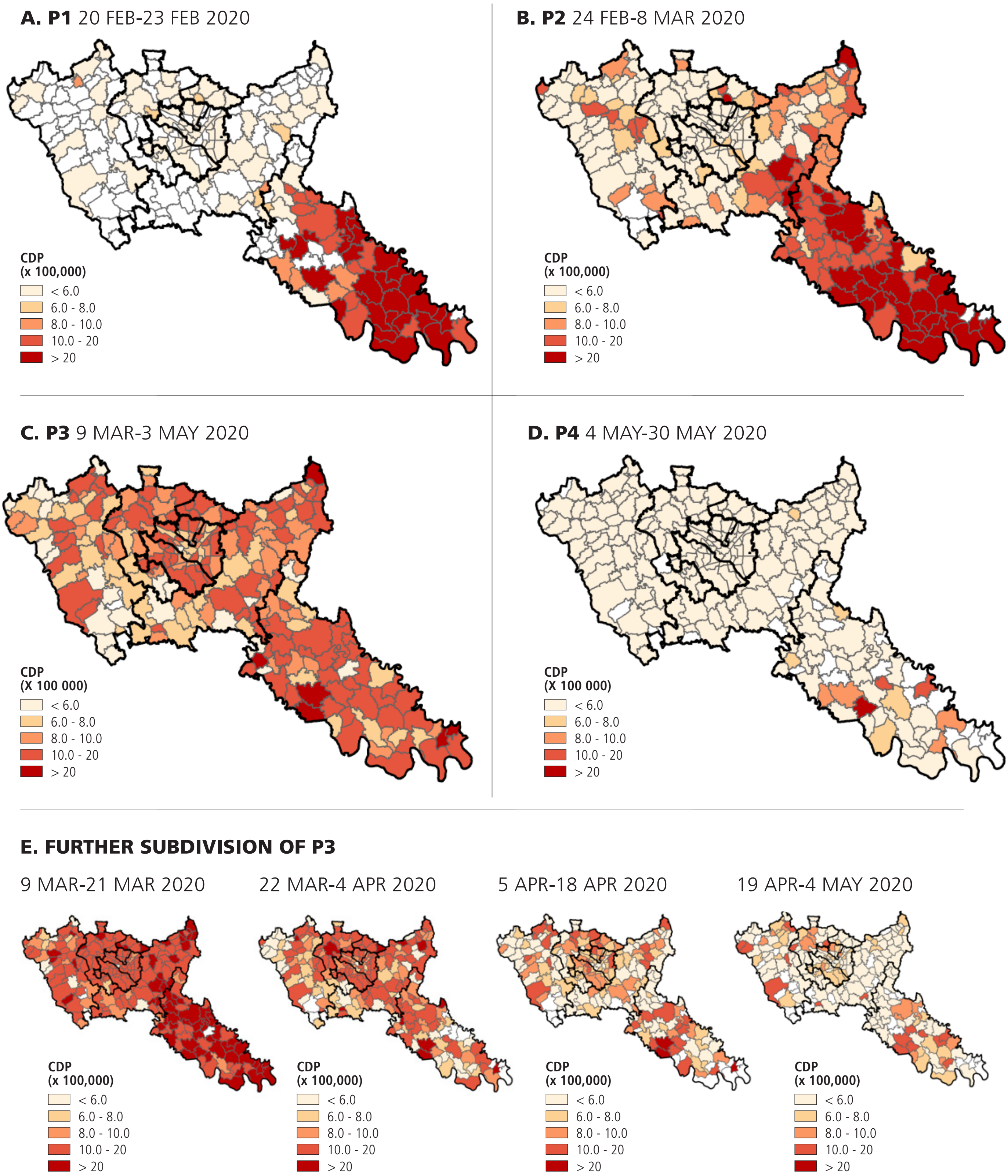
PERIOD	ASST	DAYS	CDP x100,000 (95%CI)
P1 20-23 Feb 2020	Lodi	4	26.8 (23.6-30.2)
	Melegnano		1.0 (0.7-1.5)
	Milano		0.8 (0.6-1.1)
	Nord Milano		1.5 (0.8-2.2)
	Ovest Milano		0.9 (0.5-1.3)
	Rhodense		0.8 (0.4-1.2)
	ATS		**2.7 (2.4-3.0)**
P2 24 Feb-8 Mar 2020	Lodi	14	31.5 (29.6-33.5)
	Melegnano		8.4 (7.8-9.0)
	Milano		5.0 (4.6-5.3)
	Nord Milano		8.6 (7.7-9.6)
	Ovest Milano		5.9 (5.3-6.5)
	Rhodense		4.3 (3.9-4.8)
	ATS		**7.7 (7.5-8)**
P3 9 Mar-3 May 2020	Lodi	56	13.8 (13.2-14.5)
	Melegnano		10.1 (9.8-10.4)
	Milano		10.2 (10-10.4)
	Nord Milano		12.1 (11.5-12.6)
	Ovest Milano		9.2 (8.8-9.5)
	Rhodense		10.2 (9.8-10.6)
	ATS		**10.5 (10.3-10.6)**
P4 4-30 May 2020	Lodi	27	4.6 (4.1-5.2)
	Melegnano		2.0 (1.8-2.3)
	Milano		2.4 (2.2-2.5)
	Nord Milano		2.5 (2.2-2.9)
	Ovest Milano		2.0 (1.7-2.2)
	Rhodense		1.9 (1.7-2.2)
	ATS		**2.4 (2.3-2.5)**
Epidemic period 20 Feb-30 May 2020	Lodi	101	15.1 (14.6-15.6)
	Melegnano		7.39 (7.2-7.6)
	Milano		7.05 (6.9-7.2)
	Nord Milano		8.67 (8.3-9.0)
	Ovest Milano		6.49 (6.3-6.7)
	Rhodense		6.83 (6.6-7.1)
	ATS		**7.75 (7.7-7.8)**

Table 2. Daily rate of cases (CDP) x100,000 people in Milan's ATS across the four epidemic periods.
Tabella 2. Numero di casi giorno-persona (CDP) x100.000 nella ATS di Milano nei diversi periodi epidemici per ASST

Incidence and R_t trends vary across ASSTs (Supplementary Figure S1). For the Lodi ASST, the maximum number of cases was observed during P2, on 2 March. In the other ASSTs, the peak of cases occurred in P3, and took place between 13 March (ASST West and ASST North) and 20 March (ASST Rhodense). The date on which the maximum reproduction number was recorded varies between 20 February (Lodi and Milan North) and 2 March in ASST Milan West. For certain areas (Lodi, Melegnano), the decrease in the reproduction number immediately followed identification of the first case, for other areas (Milan, North and West) the decrease occurred later. Only for the Lodi ASST, which was already a red zone, an R_t under the critical threshold of 1 was estimated before the general lockdown of 8 March (on 3 March), whereas in the other areas this result was reached later, between 22 March for ASST Milan North and 28 March for ASST Rhodense.

DISCUSSION

Overall, in the area covered by ATS-MI, incidence in the period February-May 2020 of RT-PCR confirmed COVID-19 cases was 776 per 100,000 people. This incidence is higher than the mean national incidence,[1] but lower than estimates for the entire region (913 cases per 100,000), since a higher incidence was recorded in several Lombardy areas, in particular in the provinces of Bergamo, Brescia, and Cremona.[10] The reasons why areas with high residential density like the municipalities of Milan and Monza were not affected by a comparable epidemic wave must certainly be clarified. It is likely that several factors played a protective role with respect to the spread of the virus. To date, we can only speculate that the massive shift, as early as 22 February, to remote working in third-sector businesses, which are the mainstay of Milan's economy (unlike Bergamo and Brescia, where industry is more predominant), combined with notifications by general practitioners of symptomatic cases and contacts, with recommendations to quarantine, contained the spread of the virus. It must also be borne in mind that when the lockdown was introduced (on the same date for the entire region of Lombardy, except for the red zone), the incidence of cases (per 100,000) in the city of Milan was lower than the one recorded in the provinces of Bergamo and Brescia.[1] Therefore, the restrictive regional measures and subsequent lockdown prevented the later occurrence in Milan's Metropolitan Area of a greater outbreak, comparable to the other large cities in Lombardy.
Alternative theories suggesting a greater circulation and consequent immunity of a relevant part of the population in a pre-epidemic stage, though corroborated by recent evidence that the virus was already circulating in Milan in December,[11] are not supported by the results of the seroprevalence survey of the Italian population carried out by Istat.[12] The survey estimated for the region of Lombardy a 7.5% prevalence, a value which is certainly very far from the one needed for herd immunity.
As observed in other studies,[13] in the early stages of the epidemic, the infection was prevalently diagnosed in the 60-79 year old age class. The percentage of elderly people can also be observed to double in the P3 and P4 stages of the epidemic, an effect which can be attributed, at least in part, to the spread of the epidemic in nursing homes from mid-March onward.
The greater prevalence in men at the beginning of the epidemic,[13-15] which evened out in later stages, could be explained by a selection bias of symptomatic cases tested, since several studies suggest that men have a greater risk of developing severe forms[16] of COVID-19. Furthermore, the majority of the healthcare staff[17,18] in the ATS area is female, as is the majority of residents in nursing homes[19] and sales personnel[20] in grocery shops, which stayed open; this could explain the increase in the number of infected women as the epidemic progressed.
The case fatality recorded in ATS-MI is slightly higher than



Nota: *We observe the epidemic trend in the 2 months period. After an initial phase (8-22 March) of strong widespread diffusion throughout the ATS-MI there is a progressive decrease in the second and third part of the lockdown.*

Nota: Suddividendo ulteriormente il periodo di lockdown, si può osservare il rallentamento dell'epidemia durante i due mesi. Da una fase iniziale di forte diffusione generalizzata in tutta l'ATS (8-22 marzo) si nota una diminuzione progressiva nella seconda e nella terza parte del lockdown.

Figure 4. Geographic distribution of daily cases of COVID 19 per 100,000 people during the four periods. Further subdivision (fFig. 4E) of the period from March 8 to May 30 (P3) in four intervals.

Figura 4. Distribuzione del numero di casi/giorno-persona per 100.000 abitanti nel territorio dell'ATS di Milano nelle diverse fasi epidemiche (Fig. 4A-Fig.4D) dal 20 febbraio al 30 maggio (P1-P4). Suddivisione (Fig. 4E) del periodo dall'8 marzo al 30 maggio (P3) in quattro ulteriori intervalli.

what was reported by the surveillance for Italy[1,21] and comparable to estimates reported for Lombardy[22-24] and the province of Reggio Emilia (20%).[15] The case fatality ratio in ATS-MI appears comparable to estimations made using different methods, such as time-delay adjusted case fatality (CFR 12.2; 95%CI 11.3-13.1) for the area of Wuhan (China)[25] and other estimates made outside China using WHO data (CFR 15.2; 95%CI 12.5-12.8).[26] But the case fatality remains higher, even considering individual age classes, compared to the first studies on COVID-19[27-32] and recent estimates in a number of European countries (UK 12%, Spain 6%, France 10%).[33] As expected, infection fatality ratio estimates made in the region of Lombardy[34] report a lower fatality with respect to ATS, confirming the higher risk for the population over 70 (10.5%) compared to younger subjects (0.43%). As shown in the literature, mortality is higher in men than in women,[28,35,36] although the number of women who develop the disease is greater,[11] and despite the fact that women have a higher mean age. There are various possible reasons for this difference, which could be due to a higher frequency of current or past smoking habits,[37] the more widespread presence of comorbidities, and a greater predisposition for viral respiratory infections linked to epigenetic or hormonal factors in men.[38]

Fatality analysis confirms a higher risk of death for subjects with pre-existing chronic diseases and elderly patients. This suggests the need for studies that can provide a more precise risk estimation, as well as specific detailed analysis of the causes of death. The area of the province of Lodi presents higher CFRs than the other areas of ATS-MI; this is consistent with the early and ample spread of the epidemic in the area and the substantial stress the system was under; nevertheless, the adjusted mortality analysis detected a slight, not statistically significant, excess risk, suggesting that the distribution of comorbidities in this population may have played a significant role.

Earlier studies[39,40] estimated R_0 between 1.4 and 6.5, with an average of 3.3. The variability of the estimates depends on the type of study, the epidemic stage, and the statistical methods used. The estimates for ATS-MI show an initial value (R_t 3.0), prior to the containment measures, compatible with these estimates and with the expected value for the entire region of Lombardy in the same period.[41-43] This value is lower than the one estimated in Wuhan (China) in the early stages of the epidemic ($R_{tmaximum}$ 3.8)[14] and higher than the estimate of R_0 (2.4) made before the lockdown in Vo'[44] (Padua). For all ASSTs, the progressive reduction of R_t and containment of the epidemic followed the radical measures in the reduction of social contact implemented by the region of Lombardy and the Italian government,[14,45] with the critical threshold of 1 being reached in the province of Lodi before the national lockdown. The reduction in R_t began in the days immediately following the lockdown, with the exception of ASST Rhodense, where a slower decrease in the value of R_t was observed.

The effects on the reduction in the number of cases per day-person per 100,000 people and R_t are gradual and can be seen with a delay of a few weeks; the epidemic peak was recorded during lockdown. All this is also consistent with the trends observed in Vo' [44] and can be explained with the incubation period and the possibility of intrafamily transmission.[46,47] It can also be observed that the effect of the Italian lockdown, less strict than the one imposed in China, led to a significant decrease in R_t under the critical threshold, but never reached the minimum levels (0.3) estimated for the area of Wuhan.[14] Progressive reopening took place at the end of the epidemic period, but circulation of SARS-CoV-2 is still ongoing.

CONCLUSIONS

The study allows us to make a few general observations. First of all, classic surveillance systems for infectious diseases, based on epidemiological interviews that identify cases and contacts and isolate them, work in the presence of small epidemic clusters, but can present limitations in a generalized epidemic. In this case, timely isolation of the high-risk area (Codogno's red zone) led instead to a rapid decrease in the value of R_t, suggesting that early isolation of the entire epidemic area, together with active case seeking, using testing and contact tracing, represents an effective weapon against the spread of the epidemic to surrounding areas.

The second observation refers to the possibility of early identification of the most vulnerable part of the population, which paid the highest price in terms of loss of lives, i.e., elderly people with high and specific clinical vulnerability. A model of early identification of these subjects, combined with timely care provided by general practitioners and specialists, could represent the true key to a new strategy of damage control. To that end, for subjects at higher risk, implementation of measures of prevention (for instance, reminding vulnerable subjects of the importance of observing rules of hygiene and social distancing), healthcare interventions (for example, active follow-up of patients and if necessary changes in treatment), and involvement of social services (for instance, home delivery of medical drugs and groceries) should be considered.

In conclusion, the data acquired through ***Milano COV*** allowed for the monitoring and containment of the epidemic in the area of ATS-MI. Their consistency with the findings of other studies make them a reliable information basis to carry out further evaluations on epidemic trends, identify subjects at higher risk, and assess the impact of COVID-19 on the population and the healthcare system in an area with varying degrees of urbanization and a universal healthcare system.

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