Acta Biomed 2020; Vol. 91, N. 3: e2020009 DOI: 10.23750/abm.v91i6-S.10218

Routine blood tests as an active surveillance to monitor COVID-19 prevalence. A retrospective study

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Abstract. *Background:* In Italy, one of the country most affected by the COVID-19 pandemic, the first autochthonous case appeared in Lombardy on February 20th, 2020. One month later, the number of COVID-19 patients in Lombardy exceeded 17000 and about 3500 had died. Because of this rapid increase in infected people scientists wonder whether SARS-CoV-2 was already highly circulating in Lombardy before such date. Plasma levels of aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) were shown to be highly increased in COVID-19 patients. Monitoring their levels in Emergency Room patients during the months preceding February 20th, 2020, might shade light on the prevalence of the disease in the pre-COVID-19 period. *Methods:* We retrospectively analyzed the AST and LDH levels from more than 30.000 patients admitted to the San Raffaele Hospital Emergency Room (ER) between September 2019 and May 2020 as well as between September 2018 and May 2019. The number of patients diagnosed with respiratory tract diseases were also analyzed. *Results:* Data showed that the ER averaged AST and LDH levels are highly sensitive to the presence of COVID-19 patients. During, the months preceding February 20th, 2020, AST and LDH levels, as well as the number of patients diagnosed with respiratory tract diseases were similar to their 2019 counterparts. *Conclusions:* No significant evidence showing that a large number of COVID-19 patients were admitted to the San Raffaele Hospital ER before February 20th, 2020, was found. Thus, the virus was likely circulating, within the Hospital catchment area, either in low amounts or through asymptomatic individuals. Because of the high LDH and AST levels' variations induced by COVID-19, routine blood tests might be exploited as a surveillance indicator for a possible second wave.

Keywords: COVID-19; blood test; aspartate aminotransferase; lactate dehydrogenase, surveillance

Introduction

A few months following the appearance of the coronavirus disease (COVID-19) in Wuhan, Hubei, China, a global pandemic emerged, threatening the health of the world's population. As of July 13th, the severe, acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that sustains COVID-19, has reached 213 countries, infected more than 12 million people and almost 600 thousands individuals have died as a result (1).

In Italy, one of the country most affected by COVID-19 both in term of infected people (over 240.000) and deceased (almost 35.000) (1) the first autochthonous case appeared in a small city (Codogno) near Milan (Lombardy) in a young man of 38 years old, who went to the hospital emergency room (ER) at least twice on February 18th and 19th with flu-like symptoms but was recognized as affected by COVID-19 only on February 20th (2). On March 21st, about one month later, the number of COVID-19 patients in Lombardy exceeded 17000 and about 3500 had died (2).

Furthermore, confirmed cases are thought to be underestimated due to testing not being conducted, false-negative test results (3–5) and a large number of asymptomatic or paucisymptomatic (6,7). Because of the rapid increase in infected people registered in Lombardy after February 20th, 2020, scientists and clinicians wonder whether SARS-CoV-2 was already circulating among the population before such date and if a large number of asymptomatic carriers, clinically undetected, have contributed to the rapid spread of the virus (8,9). As of writing the only scientific evidence for the presence of the SARS-CoV-2 in the Milan area before February 20th, 2020, are from a study on wastewater analysis which revealed the presence of the virus RNA in samples collected in December 2019 and January 2020 (10), and assumed that the genetic material originated from human excretions. A different approach, aiming at estimating the possible number of SARS-CoV-2 infected people in Lombardy before February 20th, 2020, based on clinical observations is difficult as COVID-19 often presents with similar symptoms to influenza (11). However, recent studies showed that several hematological parameters are markedly altered in COVID-19 patients when compared to both healthy individuals and patients with other types of respiratory tract diseases (12–17). Among them lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) were almost 50% higher in COVID-19 patients when compared to individuals with flu-like symptoms but COVID-19 negative, thus acquiring a remarkable diagnostic significance (16). Furthermore, LDH and AST are routine blood test analysis performed on almost every patient admitted at the Hospital ER. If we, reasonably, assume that COVID-19 was not present in Italy between September 2018 and May 2019, then, a comparison between the AST and LDH variations observed in a Hospital ER, in this 2018/2019 time interval, with those of the same period, but one year later, might reveal how the pandemic has evolved within the Hospitals' catchment area. Furthermore, such distinct changes in laboratory parameters, associated with a novel disease might be exploited as surveillance. Anomaly detection (i.e. the detection of events that do not conform to an expected pattern) on the pattern of routine blood analysis might predict the arrival of an epidemic and can help to save human lives. This was particularly true for the COVD-19 epidemic occurring in Europe: clinically significant changes produced by SARS-CoV-2 on several hematological parameters were known from the Chinese outbreak occurred in December 2019 (13,14) and could have been monitored in Europe as a prevention method (18). Nevertheless, predictive modeling, forecasting information from existing routine blood analysis data on COVID-19 might be exploited to prevent a possible second wave thus mitigating morbidity and mortality of the pandemic.

Herein we report the results of a retrospective study which compares the LDH and AST values measured at the San Raffaele Hospital ER between the 4th of September 2019 and the 31st of May 2020 with those measured, one year earlier, between the 4th of September 2018 and the 31st of May 2019.

Materials and Methods

Subjects

The AST, and LDH plasma levels were retrospectively analyzed in patients admitted to the San Raffaele hospital (Milan, Italy) ER between the 4th of September 2018 and the 28th of May 2019 (39 weeks) and between the 4th of September 2019 and the 27th of May 2020 (39 weeks). The time interval "4th of September 2018 - 28th of May 2019" was defined as the "non-COVID" period whereas the time interval "4th of September 2019 – 19 February 2020" and "February 20th 2020 - 27th of May 2020" were defined as the "pre-COVID" and "COVID" periods respectively. A total of 11544 and 18985 measurements were performed, respectively, for LDH and AST in the 2018/2019 period whereas a total of 13646 and 16932 measurements were performed, respectively, for LDH and AST in the 2019/2020 period. The average age of the LDH group in the 2018/19 period was 49.9 ±25.1 years old (49.2 ±25.4 and 50.7 ±26.0 years old, for females and males, respectively) whereas for AST, in the same period, was 54.4 ±25.0 years old (54.1 ±24.5 and 55.0 ±24.4 years old, for females and males, respectively). During the 2019/20 period the average age of the LDH group was 54.8 ±24.7 years old (53.7

±24.1 and 55.8 ±23.6 years old, for females and males, respectively) whereas for AST was 56.6 ±22.4 years old (55.6 ±23.7 and 57.4 ±22.7 years old, for females and males, respectively).

Individuals signed an informed consent authorizing the use of their anonymously collected data for retrospective observational studies (article 9.2.j; EU general data protection regulation 2016/679 [GDPR]), according to the San Raffaele Hospital policy (IOG075/2016).

Sample collection and analysis

Blood samples were collected as described elsewhere (19-21). AST and LDH were measured on a Roche COBAS 8000 device (Roche Diagnostic, Basel, Switzerland) using a spectrophotometric assay (22). The method for measuring AST activity, in accordance with the IFCC indications, exploit the conversion of L-aspartate and 2-oxoglutarate to L-glutamate and oxaloacetate, the latter is further converted to L-malate upon NADH consumption which is followed to determine the enzyme activity. Pyridoxal phosphate as well as NADH were added to the assay. The method for measuring LDH activity, in accordance with the IFCC indications, exploit the conversion of L-Lactate to pyruvate. The concomitant formation of NADH is proportional to the LDH activity. Hemolyzed samples were not processed. Instrumental errors, for each analyte, were monitored almost daily by averaging approximately 25-28 measurements per month (one each working day) of standard solution at low (L1) and high (L2) concentrations. The RT-PCR was performed on a Roche Cobas Z480 thermocycler using the Roche provided PCR Kit. Patients' diagnosis was from the internal San Raffaele Hospital ER database.

Statistical analyses

Statistical analyses were performed with the software Excel (Microsoft, Redmond, WA, USA). The 7-days moving average were calculated by averaging all of the AST and LDH values recorded during the 7 days preceding the calculated value. Variations of the averaged laboratory findings were expressed as 95% confidence interval.

Results

A total of 11544 and 18985 measurements were performed, respectively, for LDH and AST in the 2018/2019 period whereas a total of 13646 and 16932 measurements were performed, respectively, for LDH and AST in the 2019/2020 period. The number of LDH measurements is lower than the AST measurements because the latter is routinely performed more often. In general, 65-70% of the patients subjected to the AST test also performed the LDH examination. In contrast, a small fraction (<10%) of the LDH measurements were missing their corresponding AST tests.

To visualize the AST and LDH variation over time during the non-COVID-, pre-COVID- and COVID-periods (see materials and methods) we plot and compared the 7-days moving average of the analytes levels measured at the ER (Table 1) during these time intervals (Figure 1). The plots show that during the non-COVID-period and pre-COVID-period, both LDH and AST had a similar and essentially linear trend (Figure 1). Their averaged values, calculated during the entire non-COVID and pre-COVID intervals, were also very similar. The averaged mean AST values were 33.9±0.2 U/L and 34.3±0.9 U/L during non-COVID and pre-COVID periods respectively, whereas the mean LDH values were 253.9±2.3 U/L and 259.0±3.8 U/L during non-COVID and pre-COVID periods respectively.

In contrast, during the COVID-period, both analytes showed a prominent peak starting at February 20th, 2020, when the first Italian case was diagnosed, and ending around the 20th of April, 2020. The peaks match the plot of the number of positive RT-PCR tests recorded in the same period (Figure 1). It must be noted that the number of patients who had their blood tested for AST and LDH between February 20th and April 20th, 2020 were, respectively, 2928 and 2624 whereas those who resulted positive at the RT-PCR test, within the same time frame, were 628 (21% and 24% of the patients tested for AST and LDH respectively).

For both LDH and AST the highest point of the peak represented an increase of approximately 50% of the average value recorded during the non-COVID-period. Similar results were obtained when the

Table 1. General characteristics of patients admitted at the San Raffaele Hospital ER between September and May both in the year 2018/2019 and 2019/2020, who had their blood tested for either AST or LDH.

date	analyte	females		males		TOT (100%)	
		N (%)	age	N (%)	age	N	age
Sept 2018	**LDH**	591 (52.3)	49.3±25.0	538 (47.7)	52.3±24.8	1129	50.7±25.0
	AST	1074 (51.3)	54.3±24.3	1021 (48.7)	56.3±23.2	2095	55.3±23.8
Oct 2018	**LDH**	641 (52.3)	50.2±24.8	584 (47.7)	52.0±25.4	1225	51.1±25.1
	AST	1048 (51.4)	53.7±24.1	991 (48.6)	56.2±23.5	2039	54.9±23.9
Nov 2018	**LDH**	631 (50.4)	47.3±25.1	622 (49.6)	50.0±26.4	1253	48.6±25.8
	AST	1054 (51.3)	53.4±24.4	1000 (48.7)	54.5±24.6	2054	54.0±24.5
Dec 2018	**LDH**	649 (51.7)	48.9±26.2	607 (48.3)	50.8±27.4	1256	49.8±26.7
	AST	1089 (51.3)	54.0±24.8	1035 (48.7)	55.7±24.9	2124	54.8±24.8
Jan 2019	**LDH**	655 (52.5)	48.4±26.0	593 (47.5)	49.3±26.3	1248	48.8±26.1
	AST	1100 (52.1)	54.3±25.0	1013 (47.9)	55.1±24.8	2113	54.7±24.9
Feb 2019	**LDH**	624 (49.9)	49.2±26.0	627 (50.1)	50.4±26.6	1251	49.8±26.3
	AST	1019 (49.4)	54.0±24.0	1042 (50.6)	54.6±25.2	2061	54.3±25.0
Mar 2019	**LDH**	745 (51.6)	49.0±25.2	700 (48.4)	48.6±26.4	1445	48.8±25.0
	AST	1165 (51.8)	52.8±24.7	1084 (48.2)	53.2±24.9	2249	53.0±24.8
Apr 2019	**LDH**	693 (50.1)	50.4±25.1	689 (49.9)	51.8±25.8	1382	51.1±25.5
	AST	1075 (50.3)	54.6±24.2	1064 (49.7)	55.1±24.5	2139	54.9±24.3
May 2019	**LDH**	720 (53.1)	50.1±25.5	635 (46.9)	51.3±25.0	1355	50.7±25.3
	AST	1083 (51.3)	55.5±24.8	1028 (48.7)	54.5±23.6	2111	54.0±24.2
TOT 2018/19	**LDH**	**5949 (51.5)**	**49.2±25.4**	**5595 (48.5)**	**50.7±26.0**	**11544**	**49.9±25.1**
	AST	**9707 (51.1)**	**54.1±24.5**	**9278 (48.9)**	**55.0±24.4**	**18985**	**54.4±25.0**
Sept 2019	**LDH**	690 (52.6)	52.9±23.8	623 (47.4)	53.8±23.7	1313	53.3±23.8
	AST	951 (52.9)	55.8±23.2	847 (47.1)	56.1±22.3	1798	56.0±22.8
Oct 2019	**LDH**	829 (52.7)	52.4±24.5	744 (47.3)	53.8±25.0	1573	53.1±24.7
	AST	1121 (51.9)	55.5±23.9	1037 (48.1)	56.3±23.4	2159	55.9±23.7
Nov 2019	**LDH**	877 (51.8)	49.9±25.8	817 (48.2)	56.9±25.4	1694	53.3±25.9
	AST	1088 (51.4)	52.1±25.2	1029 (48.6)	57.3±24.4	2117	54.6±24.9
Dec 2019	**LDH**	843 (51.4)	52.4±25.5	797 (48.6)	53.0±25.5	1640	52.7±25.5
	AST	1109 (51.2)	54.9±25.2	1057 (48.8)	55.5±24.4	2166	55.2±24.8
Jan 2020	**LDH**	933 (55.0)	50.3±25.0	762 (45.0)	52.8±26.6	1695	51.4±25.8
	AST	1129 (51.3)	53.9±24.8	1072 (48.7)	55.7±25.0	2201	54.8±24.9
Feb 2020	**LDH**	796 (52.3)	49.9±25.9	725 (47.7)	51.7±25.6	1521	50.7±25.7
	AST	1010 (51.9)	53.1±25.5	937 (48.1)	54.7±24.7	1947	53.9±25.1
Mar 2020	**LDH**	472 (40.1)	56.4±21.0	682 (59.9)	59.5±18.3	1154	58.2±19.5
	AST	610 (41.7)	57.7±20.7	851 (58.3)	59.8±18.3	1462	58.9±19.4
Apr 2020	**LDH**	758 (48.9)	60.5±21.9	791 (51.1)	61.6±20.9	1549	61.1±21.4
	AST	685 (49.1)	59.3±21.8	710 (50.9)	61.1±20.8	1395	60.2±21.3
May 2020	**LDH**	693 (46.0)	58.6±23.5	814 (54.0)	59.5±21.2	1507	59.1±22.3
	AST	777 (46.1)	58.6±23.0	910 (53.9)	60.0±20.9	1687	59.4±21.9
TOT 2019/20	**LDH**	**6891 (50.5)**	**53.7±24.1**	**6755 (49.5)**	**55.8±24.1**	**13646**	**54.8±24.7**
	AST	**8480 (50.1)**	**55.6±23.7**	**8450 (49.9)**	**57.4±22.7**	**16932**	**56.6±22.4**

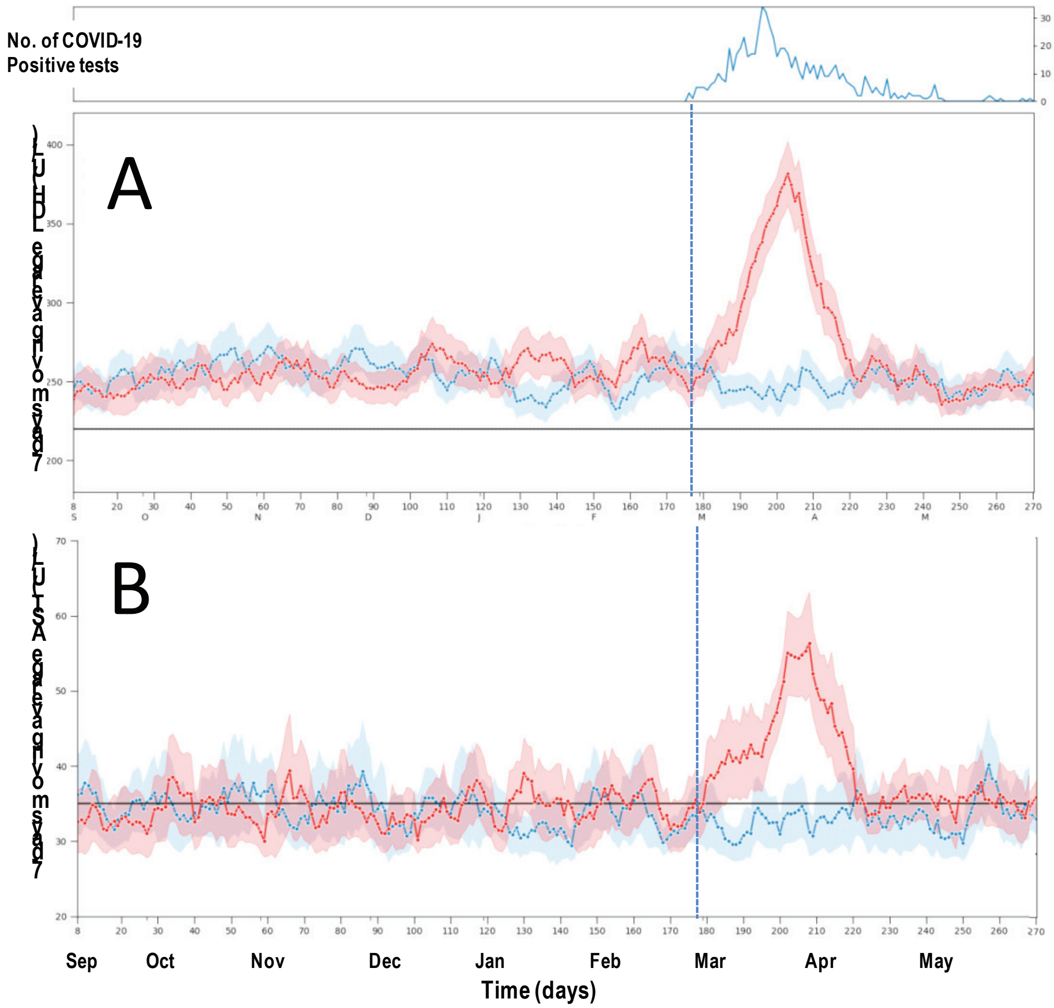

Figure 1. Panel A and B show the 7-days moving average for, respectively, LDH and AST values measured between September 2018 – May 2019 (blue line) and September 2019 – May 2020 (red line) at the San Raffaele Hospital ER. Shades represents the corresponding 95%CI. Top panel represents the number of daily positive COVID-19 cases. The vertical blue dashed lines were placed on the 19th of February when, in 2020, the first Italian autochthonous case appeared. The black horizontal lines represent the upper limit of the normal AST or LDH clinical ranges.

patients' group was further stratified by including only individuals diagnosed with a respiratory tract disease, thus presenting similar symptoms to COVID-19 (Table 2). For this restricted group of patients, the considered time interval was reduced from November 1st to March 31st. The number of patients diagnosed with respiratory tract diseases were 1340 and 1527 during, respectively, the 2018/2019 and 2019/2020 periods. Again, the averaged AST and LDH values measured in the non-COVID-period were similar to that measured in the pre-COVID one (34.9±2.4 and 36.4±2.4 U/L, for AST, and 317±13.8 and 312.6±15.8 U/L for LDH, during the 2018/2019 and 2019/2020 periods, respectively). In contrast, as seen for the totality of ER patients, during the COVID-period, the averaged AST and LDH measured only from patients affected by respiratory tract diseases were significantly higher (53.8±3.4 and 387.5±12.8 U/L for AST and LDH, respectively).

Table 2. Total number of patients admitted at the San Raffaele Hospital ER between November and March 2018/2019 and 2019/2020 (N), and number of patients who were diagnosed with a respiratory tract disease. P: pneumonia / bronchopneumonia; B: bronchitis / bronchiolitis; L: laryngitis / tracheitis; F: pharyngitis; T: tonsillitis; O: other (pulmonary edema, pulmonary embolism). Significant differences (p-value <0.05) between the same month of different years are shown (p-value).

date	N	P	B	L	F	T	O	TOT (%)	p-value
Nov 2018	5788	68	78	15	27	20	14	222 (3.8)	
Nov 2019	4743	45	33	12	12	23	14	139 (2.9)	0.0112
Dec 2018	5919	76	118	22	21	30	15	282 (4.8)	
Dec 2019	5859	64	97	12	15	25	5	218 (3.7)	0.0031
Jan 2019	6239	100	165	19	49	24	8	365 (5.9)	
Jan 2020	5711	78	86	8	46	23	13	254 (4.4)	0.0002
Feb 2019	5937	64	115	10	31	20	7	247 (4.2)	
Feb 2020	5304	106	99	19	28	19	16	287 (5.4)	0.0029
Mar 2019	6349	64	72	15	34	32	7	224 (3.5)	
Mar 2020	2588	601	7	2	8	2	9	629 (24.3)	< 0.0001

Comparing the total number of patients admitted at the ER and diagnosed with a respiratory tract disease in the different months (Table 2) revealed significant differences between each month and its one-year-later counterpart. However, the percentage of diagnosed patients is always between 2.9 and 5.9%, with the exception of March 2020 which showed a large increase in pneumonia cases bringing the percentage of respiratory tract disease patients up to 24.3% (Table 2). It must be noted that older months always showed a higher number of diagnosed respiratory tract diseases with the exception of February and March. However, if we consider only the period between the 1st and the 19th of February (pre-covid), 2019 still showed a significantly higher number of respiratory tract diseases with respect to its 2020 counterpart.

To better inquire into the general variations of both AST and LDH levels recorded on patients admitted at the Hospital ER during the pre-COVID period and its one-year earlier counterpart, we performed a statistical linear regression on the ER dataset obtained from September 4th to February 19th. Table 3 shows that during the 2018/2019 period both AST and LDH displayed a slightly, and statistically not significant, decreasing trend. In contrast, the same analysis one year later (pre-COVID-period), showed a poor, yet significant, increasing trend for both AST and LDH.

Table 3. Linear regression parameters obtained by analyzing the AST and LDH values recorded at ER during the period "September 4th - February 19th" both in the year 2018/2019 and 2019/2020. Deviation from horizontal was considered significant if the P value was <0.05.

	Equation	R^2	P value	Deviation from horizontal
LDH 2018/19	-0.44*X + 262.2	0.1007	0.1308	not significant
LDH 2019/20	0.67*X + 248.1	0.2076	**0.0253**	**significant**
AST 2018/19	-0.10*X + 35.60	0.1233	0.0925	not significant
AST 2019/20	0.10*X + 33.02	0.2475	**0.0134**	**significant**

Discussion

During the non-COVID and pre-COVID periods, the averaged AST and LDH values measured on patients admitted to the Hospital ER showed similar and substantially constant behaviors. Demographical characteristics like sex and age were also very similar in the two periods. Males and females were equally distributed, and their averaged ages were within 48 and 56 years old. The percentage of respiratory tract diseases were also similar (in term of percentages) in the two time intervals analyzed, with a slight prevalence of diagnosed patients during the 2018/2019 period. In contrast, during the COVID-period, patients admitted to ER were older (between 58 and 62 years old) and the number of respiratory tract diseases, as well as the AST and LDH averaged values, dramatically increased. An increased in AST and LDH was expected since clinical evidence showed that these parameters were markedly altered in COVID-19 patients, but remained almost unchanged in healthy individuals and patients with other respiratory tract diseases (15,16). The latter was confirmed by our study that showed similar averaged values for AST in both COVID-19 patients and patients with respiratory tract diseases from the non-COVID period. LDH levels were also lower in COVID-free patients diagnosed with respiratory tract diseases, when compared to COVID-19 patients, yet was higher than the averaged values of the whole ER population. This is consistent with the fact that LDH is recognized as a lung damage marker and is often increased in patients with severe respiratory tract diseases (22). It must be noted that within the time interval February 20th and April 20th, 2020, which approximately framed the pandemic peak, the number of COVID-19 positive patients represented less than one fourth of the total patients tested, yet, this relatively low fraction of COVID-19 positive individuals was enough to induce changes in AST and LDH up to 50% higher than the mean values measured in the pre- and non-COVID periods. This means that the averaged levels of AST and LDH, measured at a Hospital ER, were very sensitive to the presence of COVID-19 patients and can be exploited as surveillance indicators of COVID-19 prevalence among the general population of a Hospital catchment area.

Based on this assumption we thought to inquire into the problem of discriminating whether the virus was already circulating in the Milan area during the pre-COVID period and whether a number of COVID-19 patients were admitted to the ER (when the SARS-Cov-2 swab test was not yet implemented) without being properly diagnosed. The statistical linear regression showed decreasing trends for both AST and LDH between September 2018 and the 19th of February 2019. Although not statistically significant, the decrease might be consistent with another study showing an improvement of several hematological parameters, during the past few years, in the Milan area (24). In contrast, the statistical linear regression on data between September 2019 and the 19th of February 2020, showed a statistically significant increase for both AST and LDH. We might speculate that such increase was due to the presence of a small percentage of COVID-19 patients among those admitted at the ER; however, the low slope values and the relatively high *p-values* indicated that, if the latter were true, their number should have been extremely low. Further indication for a low/absent virus circulation during the months preceding the COVID-period rose from the analysis of the number of pulmonitis and other respiratory tract diseases diagnosed at ER. Data showed that December 2018, January 2019 and the first 19 days of February 2019 were actually worst (in terms of number of patients diagnosed with respiratory tract diseases), when compared to their 2019-2020 counterparts. Thus, the absence of significantly higher average values for AST and LDH before February 19th, 2020 together with the lower number of diagnosed respiratory tract diseases with respect to the previous year, seems to indicate a low virus circulation before this date.

Conclusion

Based on our data we can conclude that, before February 20th, 2020, there was no significant evidence that patients affected with COVID-19 were admitted to the San Raffaele Hospital ER. This does not mean that SARS-CoV-2 was not circulating within the Hospital catchment area before February 20th, 2020: for instance, at that time the virus could have infected, asymptomatically, individuals who did not evolve in severe cases needing admission to ER. Thus, February 19th, 2020, represents a good approximation of the beginning of the pandemic, at least in the Milan area.

Our data also showed that the high LDH and AST levels' variations induced by COVID-19 might be exploited as a surveillance indicator for the detection of a potential second (or further) wave. In this context, third-world countries, which do perform hematological tests but might not have the appropriate equipment to perform molecular tests, would greatly benefit from a surveillance test based on laboratory parameters, for instance by means of Machine Learning and Web-based services (17).

Acknowledgments: the authors acknowledge the contribution of Lorenzo Tomasoni, bachelor student of computer science, for developing some of the figures used in this manuscript according to the author's specifications.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 13 July 2020
Accepted: 20 July 2020
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