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Routine blood analysis greatly reduces the false-negative rate of RT-PCR testing for COVID-19

Davide Ferrari[1,2], Eleonora Sabetta[2,3], Daniele Ceriotti[2,3], Andrea Motta[2], Marta Strollo[2], Giuseppe Banfi[3,4], Massimo Locatelli[2]

[1]SCVSA Department, University of Parma, Parma, Italy; [2]Laboratory Medicine Service, San Raffaele Hospital, Milano, Italy; [3]Vita-Salute University, San Raffaele, Milano, Italy; [4]IRCCS Istituto Ortopedico Galeazzi, Milano, Italy

Summary. *Background:* The COVID-19 outbreak is now a pandemic disease reaching as much as 210 countries worldwide with more than 2.5 million infected people and nearly 200.000 deaths. Amplification of viral RNA by RT-PCR represents the gold standard for confirmation of infection, yet it showed false-negative rates as large as 15-20% which may jeopardize the effect of the restrictive measures taken by governments. We previously showed that several hematological parameters were significantly different between COVID-19 positive and negative patients. Among them aspartate aminotransferase and lactate dehydrogenase had predictive values as large as 90%. Thus a combination of RT-PCR and blood tests could reduce the false-negative rate of the genetic test. *Methods:* We retrospectively analyzed 24 patients showing multiple and inconsistent RT-PCR, test during their first hospitalization period, and compared the genetic tests results with their AST and LDH levels. *Results:* We showed that when considering the hematological parameters, the RT-PCR false-negative rates were reduced by almost 4-fold. *Conclusions:* The study represents a preliminary work aiming at the development of strategies that, by combining RT-PCR tests with routine blood tests, will lower or even abolish the rate of RT-PCR false-negative results and thus will identify, with high accuracy, patients infected by COVID-19. (www.actabiomedica.it)

Key words: COVID-19, RT-PCR, blood test, WBC, aspartate aminotransferase, lactate dehydrogenase

1. Introduction

A pneumonia of unknown cause, emerged in Wuhan, Hubei, China at the end of December 2019, is sustained by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19, by the World Health Organization (1). The disease rapidly spread across the globe and is now pandemic, involving 210 countries worldwide with more than 2.5 million of infected people and nearly 200.000 deaths (2), both of which are rapidly increasing.

The disease urged governments to take drastic measures like the quarantine of hundreds of millions of residents worldwide. However, because of the COVID-19 symptomatology, which showed a large number of clinically silents (3), these efforts are limited by the need of differentiating between COVID-19 positive and negative individuals.

The nucleic acid test serves as the gold standard method for the etiological diagnosis of SARS-CoV-2 infection by reversibly transcribing and amplifying, by real time reverse transcription PCR (RT-PCR), the virus genetic material possibly present on respiratory tract specimens. Thus, RT-PCR is often used as the main indicator for patients' isolation, transferring into the appropriate hospital department and final discharge provided that two consecutive RT-PCR tests, at least 24 hours apart, result negative (4).

However, it was reported in several recent studies, that the RT-PCR test on COVID-19 exhibited a high

rate of false negative results which, in some cases was as large as 20% (4–9) we present chest CT findings from five patients with 2019-nCoV infection who had initial negative RT-PCR results. All five patients had typical imaging findings, including ground-glass opacity (GGO. This could be caused by a low viral loads in the initial phase of infection (8) and is sustained by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, nevertheless, diagnostic errors may also arise from other sources like the pre-analytical thermal inactivation of samples (10), wrong sample collection or transportation (8) and is sustained by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or a non-specific PCR primers annealing due to virus mutation and recombination (11).

Considering the strong infectivity of COVID-19, a false negative rate as large as 20% represents a large disadvantage because patients need to be accurately identified, isolated and treated as soon as possible in order to reduce mortality rates and the risk of public contamination. A few recent studies proposed computer tomography (CT), which showed a sensitivity of 97.2%, as a better diagnostic tool for COVID-19 (7,12) who were examined by both CT and rRT-PCR at initial presentation. The sensitivities of both tests were then compared. For patients with a final confirmed diagnosis, clinical and laboratory data, in addition to CT imaging findings were evaluated. Results: A total of 36 patients were finally diagnosed with COVID-19 pneumonia. Thirty-five patients had abnormal CT findings at presentation, whereas one patient had a normal CT. Using rRT-PCR, 30 patients were tested positive, with 6 cases initially missed. Amongst these 6 patients, 3 became positive in the second rRT-PCR assay (after 2 days, 2 days and 3 days respectively. However, the use of CT as a diagnostic tool can be exploit only in patients with acute pulmonary symptoms, which are on average 10% of the total infected people (2).

We recently showed that several hematological parameters were significantly altered in COVID-19 patients when compared with patients having similar symptoms, but COVID-19 negative (13, 14) the epidemic has gradually spread to 209 countries worldwide with more than 1.5 million infected people and 100,000 deaths. Amplification of viral RNA by rRT-PCR serves as the gold standard for confirmation of infection, yet it needs a long turnaround time (3-4 h to generate results. By empirically using cutoff levels for lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) we were able to identify, in a group of 207 patients, COVID-19 positivity/negativity in almost 70% of the them with predictive values as large as 90%. Thus, by combining RT-PCR with routine blood test, the rate of false-negative might be greatly reduced.

In this retrospective study we randomly selected 24 patients, were admitted to the San Raffaele Hospital (Milan, Italy) emergency room (ER) with COVID-19 symptoms, who showed either dubious baseline RT-PCR tests or discrepant results between baseline and follow-up measurements. In these patients we compared the number of false-negative results obtained with RT-PCR and routine blood test upon admission to the E.R.

2. Materials and Methods

2.1 Subjects

The AST, and LDH plasma levels were retrospectively analyzed and related to their corresponding RT-PCR tests in a group of 24 patients (6 females and 18 males), who were admitted to the San Raffaele hospital (Milan, Italy) emergency room between the 1st of February and the 7th of April 2020 as suspected COVID-19 patients. The 24 patients were retrospectively and randomly selected (alphabetical order) based on: 1) the presence of multiple RT-PCR tests in the first phase of hospitalization, 2) inconsistency between the RT-PCR test performed on admission to ER (day zero) and later tests, 3) the availability of routine blood examination results. The average age was 64.6 ±13.4 years old (58.7 ±10.2 years old and 67.2 ±15.0 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).

2.2 Sample collection and analysis

Blood samples were collected as described elsewhere (14,15) low vitamin D status is common in Europe even at mid-latitudes. The UV-radiation that reached the Earth's surface near Milan between May 2006 and December 2018 was retrieved from the TEMIS database and matched with the serum vitamin D levels measured in 30400 people living in the same area. The results showed a high percentage of insufficient vitamin D levels (measured as 25-hydroxy-vitamin D. AST and LDH were measured on a Roche COBAS 8000 device (Roche Diagnostic, Basel, Switzerland) using a spectrophotometric assay (16) 35 immunochemical and 7 serology analytes in a BD-Vacutainer® Barricor tube for local clinical validation of this lithium-heparin tube with a barrier. METHODS: Samples from 70 volunteers were collected in different BD-tubes: a clot-activator tube with gel (SST. The method for measuring AST activity, in accordance with the IFCC indications, exploit the conversion L-aspartate and 2-oxoglutarate to L-glutamate and oxalacetate which 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 L-Lactate to pyruvate. The concomitant formation of NADH is proportional to the LDH activity. Hemolyzed samples were not processed, thus all of the data represents samples with no clear sign of hemolysis.

RT-PCR was performed on a Roche Cobas Z480 thermocycler (Roche Diagnostic, Basel, Switzerland) using the Roche provided Tib-Molbiol's 2019-nCoV Real-Time Reverse Transcription PCR Kit. RNA purification was performed using the Roche Magna pure system. A cycle threshold value (Ct value) lower than 37 was defined as a positive result, whereas a Ct-value above 40 was defined as a negative test. Ct-values between 37 and 40 were considered dubious results.

2.3 Statistical analyses

Statistical analyses were performed with the software Excel (Microsoft, Redmond, WA, USA).

3. Results

Between the 1st of February and the 7th of April 2020, the laboratory medicine service of the San Raffaele Hospital in Milan performed 8803 RT-PCR swab tests (Table 1). The 35.6% of them were positive while the 52.7% and 11.6% were, respectively, negative, or with a dubious outcome. Of the 8803 tests, 1176 were form the ER which showed a percentage of positive RT-PCR as large as 47.6% (560 positive tests, Table 1). Of the 560 positive patients, 66.1% were males and 33.9% were females (Table 1). Approximately 40% of the patients admitted to the ER (data not shown) were later hospitalized thus receiving several RT-PCR test needed to monitor the course of the disease. Among these we randomly selected 24 patients, having available routine blood tests results, who showed inconsistent RT-PCR tests when compared to that obtained upon admission to ER. Patients' baseline characteristics were listed in Table 2 while Ta-

Table 1. Number of RT-PCR tests performed at the San Raffaele Hospital laboratory between the 1st of February and the 7th of April 2020. Percentages were calculated as a fraction of the total tests (last column). "All" represents the entire tests performed whereas "ER" represents the test performed upon admission to the Emergency Room

	Males				Females				Total			
	P	**N**	**D**	**TOT**	**P**	**N**	**D**	**TOT**	**P**	**N**	**D**	**TOT**
All	1905	2272	574	4751	1230	2371	451	4052	3135	4643	1025	8803
%	21.6	25.8	6.5	54.0	14.0	26.9	5.1	46.0	35.6	52.7	11.6	100
ER	370	263	83	716	190	220	50	460	560	483	133	1176
%	31.5	22.4	7.1	60.9	16.2	18.7	4.3	39.1	47.6	41.1	11.3	100

Table 2. Baseline and clinical characteristic of the study population upon admission to ER

Patient	Sex	Age	Symptoms	Temp. (C°)	pO_2 (%)
1	M	61	Dyspnoea	38.8	94
2	M	73	Dyspnoea, cough, fever	37.7	96
3	F	69	Fever, vomit, diarrhea	37.2	95
4	M	57	Fever	37.2	97
5	M	63	*	*	*
6	M	49	Dyspnoea, fever	36.8	97
7	M	54	Chest pain	38	100
8	F	55	Fever, asthenia	38.4	88
9	M	76	Dyspnoea, cough, fever	36.6	82
10	M	42	Fever	39	97
11	F	43	Dyspnoea	37.5	*
12	M	54	Dyspnoea, fever	38	94
13	F	54	Fever, syncope	37.7	98
14	M	72	Fever	37	91
15	M	86	Dyspnoea, fever, cough	37.7	90
16	F	70	Cough, fever	38	95
17	M	79	Cough, fever	36.8	89
18	M	85	Fever	36	*
19	M	49	Asthenia	38.3	*
20	M	88	Syncope	36	98
21	M	76	Cough, fever	38.9	85
22	M	74	Dyspnoea, syncope	38	88
23	M	61	Dyspnoea, tachypnea, diarrhea	39	70
24	F	61	Fever	36	99
Average		64.6±13.4		37.6±0.9	92.1±7.1

*missing data from ER

ble 3 showed the different RT-PCR tests' results, the number of days between them, and the AST and LDH serum level recorded in the initial hospitalization period. Fourteen patients (patients 2, 3, 5, 8, 10, 11, 12, 15, 18, 19, 20, 22, 23 and 24) had a positive RT-PCR result after a negative one at ER admission (Table 3). The time interval between the negative and the positive tests was between 1 and 7 days (Table 3). In a previous work based on more than 200 patients (13) the epidemic has gradually spread to 209 countries worldwide with more than 1.5 million infected people and 100,000 deaths. Amplification of viral RNA by rRT-PCR serves as the gold standard for confirmation of infection, yet it needs a long turnaround time (3-4 h to generate results, we showed that when both AST and LDH levels were above, respectively, 35 and 210 U/L, the individual has a probability higher than 83% of being COVID-19 positive, whereas a AST level lower than 25 U/L is consistent with a probability higher than 90% of being COVID-19 negative. Patients with AST between 25 and 35 U/L were considered dubious (13) the epidemic has gradually spread to 209 countries worldwide with more than 1.5 million infected people and 100,000 deaths. Amplification of viral RNA by rRT-PCR serves as the gold standard for confirmation of infection, yet it needs a long turnaround time

Table 3. RT-PCR tests and AST/LDH levels of the 24 patients involved in the study. RT-PCR tests were color coded: white cells (negative), light grey cells (dubious) dark grey cells (positive). AST and LDH were color coded according to [13]. white cells (AST<25 U/L, negative), light grey cells (AST between 25 and 35 U/L, dubious) and dark grey cells (AST>35, LDH>210 U/L, positive). The time interval (days) between the different RT-PCR tests was als

	day	RT-PCR	AST	LDH
Patient 1	0	doubt	33	419
	2	doubt	30	392
	7	positive		
Patient 2	0	negative	31	247
	1		52	347
	3	positive		462
Patient 3	0	negative	16	237
	3	positive		
Patient 4	0	doubt	25	
	1	doubt		
	4		36	333
	12	positive	30	287
Patient 5	0	negative	43	224
	1	positive		
Patient 6	0	doubt	27	257
	2	positive		
Patient 7	0	doubt	72	461
	3	negative		
Patient 8	0	negative	55	509
	1	positive	79	473
Patient 9	0	doubt	38	453
	1	doubt	29	387
	2	doubt	41	507
	6	negative		
	8	negative		
Patient 10	0	negative	46	298
	3	positive		
Patient 11	0	negative	36	347
	5	positive	45	328
Patient 12	0	negative	45	354
	1	positive		

	day	RT-PCR	AST	LDH
Patient 13	0	doubt	89	307
	6	negative	43	
	8	positive		
Patient 14	0	doubt	48	539
	4	positive	46	527
Patient 15	0	negative	21	177
	2	positive	44	181
	11		37	245
Patient 16	0	doubt	19	282
	1	negative	13	210
	4	negative		
	6	negative		
Patient 17	0	doubt	113	439
	1	doubt		
	2	positive	86	416
Patient 18	0	negative	59	682
	2	positive	54	546
Patient 19	0	negative	44	323
	2	positive	41	311
Patient 20	0	negative	28	630
	3	positive		
Patient 21	0	doubt	59	
	4	negative	73	525
Patient 22	0	negative	61	444
	3	positive	55	538
Patient 23	0	negative	52	955
	1	doubt	39	882
	7	positive	84	625
Patient 24	0	negative	59	291
	2	positive	33	215

(3-4 h to generate results. Among these 14 patients, 10 of them (patient 5, 8, 10, 11, 12, 18, 19, 22, 23 and 24) had both AST and LDH, upon admission to ER, above the suggested threshold thus, based on their blood tests, they were most likely COVID-19 positive (Table 3). In contrast, patient 2 and 20 had AST between 25 and 35 at ER admission, thus, they could not be classified as either COVID-19 positive or negative. However, the following day patient 2 had both AST and LDH above the threshold (thus consistent with COVID-19 positivity) while a positive RT-PCR test was available only on the third day of hospitalization. Furthermore, both patient 2 and 20 showed high levels of LDH at day 0 (Table 3). Patient 3 and 15 had, on admission to ER (day 0, Table 3), hematological parameters consistent with COVID-19 negativity (AST<25 U/L). Yet, patient 3 had a high LDH level whereas patient 15 showed raising levels of both AST and LDH during the first hospitalization period. Such levels became consistent with COVID-19 positivity at day 11 while the RT-PCR test turned positive already on day 2 (Table 3). Unfortunately, AST and LDH data between day 2 and day 11 were missing for patient 15.

The remaining 10 patients (patient 1, 4, 6, 7, 9, 13, 14, 16, 17 and 21) had a dubious result (see materials and methods section) on their first RT-PCR tests (Table 3). By considering their hematological parameters, six of them (patients 7, 9, 13, 14, 17 and 21) had, at day 0, AST and LDH above the threshold levels (LDH was missing at day 0 for patient 21. Table 3), thus consistent with COVID-19 positivity. The hematological inferred positivity were later confirmed by RT-PCR for patient 13, 14, and 17, whereas patients 7, 9 and 21 had negative results. Patient 1, 4 and 6 had, at ER admission, AST between 25 and 35U/L thus, they could not be classified as either COVID-19 positive or negative. Yet, patient 1 and 6, for which COVID-19 positive RT-PCR tests were obtained after 7 and 2 days respectively, had high LDH levels at day 0. Patient 4, for which LDH data was missing at day 0, had both AST and LDH above the threshold on day 4 and thus consistent with a COVID-19 positivity which was later confirmed by RT-PCR on day 12 (Table 3). Patient 16, after a dubious RT-PCR test had three consequently negative results. The blood test showed a AST level below 25 U/L, thus consistent with COVID-19 negativity, which was sustained on day 1 by a further decrease of both AST and LDH (Table 3).

4. Discussion

Among the 8803 RT-PCR tests performed during the study period, 35.6% resulted positive while 52.7% and 11.6% were respectively, negative and dubious. The percentage of positive tests is much higher in the ER subset (approximately 50% of positive RT-PCR tests) because the whole batch contains tests also from medical personnel and workers who needed to be tested, even without symptoms, for social safety reasons. In addition, the whole batch contains RT-PCR from the many hospitalized people who, once the course of the disease is over, will account for a large number of negative RT-PCR tests needed for their discharge. In contrast, the batch from the ER refers to patients with symptoms that after a routine visit, which usually includes also a blood test, were PCR-tested only once and then either sent home or hospitalized. The percentage of dubious test, approximately 11.5%, is very similar in the two batches (Table 1), highlighting the limitations of this type of diagnosis (8) and is sustained by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2. Among the 24 randomly chosen patients, 14 of them showed false-negative RT-PCR tests upon admission to ER and, based on such results, they would be placed in a NON-COVID-19 department until the second RT-PCR test proves the inaccuracy of the previous one. Table 3 shows that a patient could spend as much as 7 days (patient 23) before being placed in a COVID-19 department and that the average time spent in the "wrong" department is 2.7 days (data not shown). Considering the strong infectivity of COVID-19, this represents a high risk of contamination outbreak which may jeopardize the health of other recovered patients, medical personnel and visitors. The remaining 10 patients had a dubious RT-PCR results. One of them (patient 13) had a second and negative RT-PCR test six days later but, after two more days (day 8), the third RT-PCR test turned out to be positive representing a further example of false-negative RT-PCR test. Again, such patient, if hospi-

talized in the wrong department, could be a source of an outbreak of infection. Among the 10 patients with a doubtful initial result, the waiting time before receiving a positive/negative result could be as long as 12 days (patient 4), with an average of 4.7 days (data not shown). Thus, based on the RT-PCR tests, 15 patients (62.5%) would have been hospitalized in the wrong COVID-19 department whereas the remaining 9 patients (37.5%), in the best of cases, will be isolated for several days waiting for a certain response. In contrast, if we based the differentiation between COVID-19 positive and negative patients only on the AST and LDH serum levels, 15 (62.5%) out of 24 patients would have been hospitalized in the correct department at day 0, five patients (20.8%) would have had a dubious results and 4 patients (16.7%) would have been wrongly diagnosed. This represent an error rate almost 4-fold lower than the genetic test (62.5% vs. 16.7%). Furthermore, three of the patients with dubious results (AST between 25 and 35 U/L) had high level of LDH indicating a likely (and later confirmed) positivity for these patients.

It must be noted however, that possible AST fluctuations due to vitamin b6 deficiency cannot be excluded as this type of analysis is not required in individuals admitted to the emergency room as suspected COVID-19 patients. In contrast, hemolysis did not affected our data because samples showing sign of hemolysis were not processed in our laboratory.

This comparison was made possible by the presence of hospitalized patients with multiple and inconsistent RT-PCR test. However, the majority of the patients (60%) admitted to the ER had symptoms that did not require hospitalization, and were sent home. Of them, almost 40% (data not shown) had a negative results. Considering the 10-15% rate of false-negative RT-PCR tests for COVID-19 (4–9) we present chest CT findings from five patients with 2019-nCoV infection who had initial negative RT-PCR results. All five patients had typical imaging findings, including ground-glass opacity (GGO, a large number of individuals would be sent home with an erroneous diagnosis and could unawarely infect other people, making the restrictive measures taken by governments, worthless.

What we propose is a combination of RT-PCR test and routine blood test to minimize the risk of inadvertently diagnosing COVID-19 positive patients as negative. To minimize the risk upon a negative RT-PCR test at day 0, the clinician should verify whether the AST and LDH levels are in agreement with the genetic test. If not, a second RT-PCR should be performed as soon as possible to avoid misdiagnosis. In case of a dubious RT-PCR result at day 0, current clinical practices already suggest a second test as soon as possible, however, taking into consideration the AST and LDH serum levels could give a preliminarily positivity/negativity indication useful for the patients' management in the ER.

5. Conclusion

The well- known high rate of false-negative RT-PCR test for COVID-19 (4–9) we present chest CT findings from five patients with 2019-nCoV infection who had initial negative RT-PCR results. All five patients had typical imaging findings, including ground-glass opacity (GGO could be one of the reason for the slow decrease of infected cases in several countries and may jeopardize a rapid return to normal life. We demonstrated that the rate of false-negative RT-PCR tests was lowered by almost 4-fold by when the AST and LDH hematological levels were used synergistically with the genetic test. In a previous work (13) the epidemic has gradually spread to 209 countries worldwide with more than 1.5 million infected people and 100,000 deaths. Amplification of viral RNA by rRT-PCR serves as the gold standard for confirmation of infection, yet it needs a long turnaround time (3-4 h to generate results we showed that, in addition to AST and LDH, white blood cells (and subtypes), c-reactive proteins and alanine aminotransferase were also indicators of COVID-19 positivity. We believe that by using appropriate software able to combine the RT-PCR tests with routine blood analysis it should be possible to lower or even abolish the rate of RT-PCR false-negative results and thus identify, with high accuracy, patients infected by COVID-19.

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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Correspondence:
Davide Ferrari
SCVSA Department, University of Parma, Parma, Italy
Tel. +39 0521 906633
Fax +39 0521 905151
E-mail: davide.ferrari@unipr.it