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ORIGINAL ARTICLE

Adaptation of Clinical Laboratories to COVID 19 Pandemic: Changes in Test Panels, Overcoming Problems and Preparation Suggestions for Future Pandemics Adaptation of Clinical Laboratories to COVID 19 Pandemic

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SUMMARY

Background: **For Coronavirus Disease 2019 (Covid-19) infection, clinical laboratories provide essential contributions in the diagnosis of infection, stage prognostication, and evaluation of disease severity. We aimed to show laboratory problems including changes of test numbers, changes of test panels, and differences of preanalytical errors during Covid-19 pandemic and, in the current study, we also intended to give solutions for the obstacles to guide other possible pandemics.**
Methods: **Our study was based on data between January 10, 2020, and May 10, 2020. The first Covid-19 case of the Republic of Turkey was seen March 10, 2020, which was determined as the threshold date for comparisons. This was a single center, data mining, retrospective study.**
Results: **The number of patients admitted to hospital were 34,260 and 15,573, the number of total tests were 66,263 and 42,066 before and after pandemic, respectively, for the two-month interval. Test percentage changes were increased for D-dimer 136%, fibrinogen 3,113%, troponin 6%, and LDH 17%. Test percentage changes were decreased for CBC 37%, sedimentation 45%, aPTT 30%, PT 37%, CRP 28%, ProCT 10%, ferritin 29%, CK-MB 27%, blood gases 47%, ALT 43%, AST 42%, urea 42%, creatinine 42%, triglycerides 45%, sodium 42%, potassium 41%, chloride 21%, urine culture 58%, and blood culture 44%. When preanalytical sources of errors were investigated no differences were found.**
Conclusions: **Laboratories must take quick action and be prepared for changes in patient services during pandemics. The most reliable ways for this are past experiences, statistical analysis, co-operation with administrations, high quality communication skills, and a risk-based management system.**
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KEY WORDS

Covid 19, clinical laboratory problems, pandemic, preanalytical errors

LIST OF ABBREVIATIONS

ARDS - Acute respiratory distress syndrome
AIDS - Acquired Immune Deficiency Syndrome
ALT - Alanine Aminotransferase
AST - Aspartate Aminotransferase

CRP - C-reactive protein
Covid-19 - Coronavirus Disease 2019
DIC - Disseminated Intravascular Coagulation
LDH - Lactate Dehydrogenase
MERS - Middle East Respiratory Syndrome
ProCT - Procalcitonin
RT-PCR - Reverse Transcription-Polymerase Chain Reaction
SARS - Severe Acute Respiratory Syndrome
SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2

INTRODUCTION

Although hopes increased after Fleming's penicillin discovery in the first half of the twentieth century, epidemic diseases still pose a major threat to human health in the 21st century [1]. Laboratory medicine supplies fundamental contributions for estimating susceptibility to diseases, anticipating diseases, classification of risk factors, therapeutic monitoring, diagnosing many pathological conditions at early stages, observing disease progression, personalizing treatments, and care management in most diseases including infectious diseases such as coronavirus disease 2019 (Covid-19) [2-5]. Medical laboratories, which have even more critical importance in the current health system compared to the past, have great responsibilities during pandemics. In the 20th century, Poliomyelitis [6,7], Spanish Influenza Flu (H1N1) [8], Asian Influenza (H2N2) [9], Acquired Immune Deficiency Syndrome (AIDS) [10], and in the 21st century Severe Acute Respiratory Syndrome (SARS) [11,12], Middle East Respiratory Syndrome (MERS) [13], Ebola virus disease [14] and Zika virus infection [15] are accepted as pandemics or endemic diseases of certain districts. Convalescent serum preparation, respiration analysis, cerebrospinal fluid analysis, renal function evaluation, specific IgG detection, reverse transcription-polymerase chain reaction (RT-PCR) tests, molecular analysis, and antibody tests are some examples of clinical laboratory contributions.

Epidemic SARS coronavirus-2 (SARS-CoV-2) that causes coronavirus disease 2019 is a novel coronavirus was initially detected in Wuhan, China in the final days of 2019 [16]. Since the first detection of the virus on 10 March 2020, more than 120,000 cases of Covid-19 have been confirmed in Turkey by May 2020. A real-time reverse-transcription polymerase chain reaction (rRT-PCR) is available to identify the virus. In addition, anti-Covid-19 antibodies can be determined by fully-automated immunoassays devices. In Covid-19 infection, essential contributions of clinical laboratories are to provide definite diagnosis of infection as well as stage prognostication, evaluation of disease severity, prediction of risk progression to sepsis, acute respiratory distress syndrome (ARDS) or disseminated intravascular coagulation (DIC), treatment response, and community observations in distinct areas [17]. Lippi et al. [18] showed main laboratory abnormalities in Covid-19 infection. White blood cell count, neutrophil count, C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), total bilirubin, creatinine, cardiac troponin, D-dimer, prothrombin time (PT), procalcitonin (ProCT) showed increased levels while lymphocyte count and albumin showed decreased levels. There are national as well as international guidelines. Data from clinical laboratories have critical roles during follow up of patients in the guideline published by the Republic of Turkey Ministry of Health, which was very successful in combating the pandemic. It is recommended that the physician requests complete blood count, CRP, ProCT, renal function tests (blood urea nitrogen and creatinine), hepatocyte function tests, cardiac enzymes, LDH, fibrinogen, D-dimer, ferritin, arterial blood gas, and lactate analysis for patients with suspicion of Covid-19. According to the aforementioned guideline, blood lymphocyte count < 800/μL, CRP > 40 mg/L, ferritin > 500 ng/mL and/or D-dimer > 1,000 ng/mL have been reported as poor prognostic measures [19]. Deng et al. [20] conducted a retrospective study to analyze the clinical and laboratory characteristics of fatal cases and recovered patients with Covid-19. They concluded that the death group showed increased WBC count, decreased lymphocytes, and elevated CRP levels compared to the recovered patients. It is also recommended to use clinical laboratory data in the diagnosis of macrophage activation syndrome, patient transfer decision to intensive care units, diagnosis of sepsis, coagulopathy analysis, and tociluzumab treatment.

Effective laboratory organization is very important in pandemics such as Covid-19 [17]. The daily activity of clinical laboratories can be quickly saturated or interrupted with more tests than the laboratory capacity [17]. In our current study, all laboratory processes were evaluated based on medical laboratory and hospital statistics including changes of test numbers, changes of test panels, and differences of preanalytical errors before and after reports of the first cases of Covid-19 positive patients. We aimed to show laboratory problems during Covid-19 pandemic and we also intended to give solutions for the obstacles to guide future pandemics.

MATERIALS AND METHODS

Local Clinical Ethics Committee of Istanbul Maltepe University Faculty of Medicine approved the study protocol 2020/900/35. This retrospective investigative data mining study was guided by strict evaluation of laboratory and hospital information systems at the same time and evaluated by a blinded statistician and laboratory physicians. Our study was based on data between January 10, 2020, and May 10, 2020. First Covid-19 case of the Republic of Turkey was seen March 10, 2020, which was determined as the threshold date for comparisons. Bio statistical information was analyzed using

Microsoft Excel 2010® (Microsoft Corporation, USA) and SPSS v 21.0® (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY, USA). Mean, median, and standard deviations of the results were calculated. Unpaired *t*-test and chi square independence tests were used for comparing quantitative and qualitative variables respectively [21]. $p < 0.05$ was considered statistically significant. Formulas for outpatient admissions and hospitalized patients test ratio change percentage calculations were presented in Figure 1A and 1B. Comparisons were given as percentages because they were studied over two different time periods.

RESULTS

The number of patients admitted to our hospital were 34,260 and 15,573, the number of total tests were 66,263 and 42,066. The average number of tests per single patient were 1.8 and 2.6 before and after pandemic, respectively, for the two-month interval (Table 1). First striking information showed that although the number of patients decreased, the number requested tests of patients increased (average number of tests per patient changed from 1.8 to 2.6). Test percentage changes were increased for D-dimer 136%, fibrinogen 3,113%, troponin 6%, and LDH 17%. Test percentage changes decreased for CBC 37%, sedimentation 45%, aPTT 30%, PT 37%, CRP 28%, ProCT 10%, ferritin 29%, CK-MB 27%, blood gases 47%, ALT 43%, AST 42%, urea 42%, creatinine 42%, triglycerides 45%, sodium 42%, potassium 41%, chloride 21%, urine culture 58%, and blood culture 44%. Test ratio percentage changes for outpatient admissions and hospitalized patients were also calculated in Table 2A, 2B, and 2C (Table 2). When preanalytical sources of errors were investigated, incorrect sample type 0.01% and 0.01%, hemolysis 10% and 8%, clotted sample 0.4% and 0.4%, inappropriate sample type 0.07% and 0.001% were found before and after pandemic, respectively, for the two-month interval (Table 3).

DISCUSSION

The situation can be challenging for the laboratories that are active in this pandemic period. While trying to work with "The right test, right method, and correct result" principle, what can be done in extraordinary times can be confusing. Possible confusing and/or potentially troublesome elements in the pandemic process can be listed as follows:

a) change of general health system functioning
b) quantitative changes in test requests
c) health status of laboratory professionals, possible extra assignments
d) extra precautions for differences in infective rates for different sample types
e) request for mobile laboratory establishments in different locations
f) major changes in test panels
g) requests for new test addition
h) false positive or negative ratios of new tests
i) urgent validity of new test methods
j) health care professionals' shift systems
k) expiration date, kit, and equipment storage tracking changes
l) test run and approval process (turnaround time) shortening request

Undoubtedly, some of these issues were predictable and we had a solution in the short term. Our hospital was declared as a "pandemic hospital" and still is. This created changes in our laboratory work system at the beginning. The number of workers and shift systems were revised and personal protective equipment were checked more frequently. But the first and perhaps most important lesson from Covid-19 pandemics is to increase the volume of some tests to manage emerging conditions [22]. Distinctive increase in the number of tests per tube and per patient proved this data, as well (Table 1). Our study indicated that laboratories should increase test stocks especially for D-dimer, fibrinogen, troponin, and LDH (Table 2A, 2B, 2C). Tang et al. [23] investigated coagulation parameters in severe coronavirus pneumonia patients and they concluded that increased levels of D-dimer and fibrin degradation product could predict mortality in coronavirus pneumonia patients. Zhang et al. [24] investigated D-dimer levels on admission in Covid-19 positive patients. They concluded that D-dimer levels higher than 2.0 µg/mL could effectively predict mortality in Covid-19 positive patients. Elevated troponin levels were found with increased mortality rate which can be explained by myocarditis, acute myocardial infarction, myocardial injury or microangiopathy in Covid-19 positive patients [19,25-28]. These studies and guidelines provided a dramatic increase in these parameters during pandemic period. When cultures were considered, it was observed that even though the number of total culture requests decreased, the ratio of requests increased in outpatients. This situation can be explained by the fact that patients who did not want to come to hospitals due to the epidemic, although they need to stay in the hospital, tended to take home care health services. After the number of tests, the second noticeable change was the changing of the laboratory panels that physicians wanted from laboratories to work. Although the change of test request habits takes a long time at normal times, we observed these changes very quickly. In our study, we evaluated the test request panels in two forms as outpatients and inpatients. When Table 2 is examined in detail, an increase was observed in almost all tests for outpatient clinics. However, the situation was different for hospitalized patients. D-dimer, fibrinogen, ProCT, troponin, and LDH test requests increased in proportion to inpatients due to the recommendations in the guidelines described during pandemics. However, a remarkable issue here is that there was increased demand for these tests even in rou-

Table 1. Average number of tests, biochemistry and immunoassay tests per tube, number of patients and tests during two time periods.

	January 10, to March 10, 2020	March 11, to May 10, 2020
Average number of immunoassay tests per single tube	4	5
Average number of routine biochemistry tests per single tube	13	19
Average number of tests per single patient	1.8	2.6
Average number of patients admitted to the hospital	34,260	15,573
Total number of tests	66,263	42,066

Table 2A, 2B, 2C.

2A

	CBC	ESR	aPTT	PT	D-dimer	Fibrinogen	CRP	ProCT
January 10, to March 10, 2020	8,286	2,494	1,609	1,877	301	8	4,458	1,207
March 11, to May 11, 2020	5,236	1,365	1,129	1,190	711	257	3,204	1,081
Total test percentage changes	-37%	-45%	-30%	-37%	+136%	+3,113%	-28%	-10%
Outpatient admissions/test ratio change percentage	+72%	+49%	+91%	+72%	+542%	+8,636%	+95%	+144%
Hospitalized patient/test ratio change percentage	-27%	-37%	-19%	-27%	+174%	+3,622%	-17%	+4%

2B

	Ferritin	Troponin	CK-MB	Blood gases	ALT	AST	Urea	Creatinine
January 10, to March 10, 2020	1,217	792	901	345	6,247	6,199	6,322	6,570
March 11, to May 11, 2020	862	842	660	182	3,566	3,582	3,639	3,783
Total test percentage changes	-29%	+6%	-27%	-47%	-43%	-42%	-42%	-42%
Outpatient admissions/test ratio change percentage	+93%	+189%	+99%	+43%	+55%	+57%	+57%	+57%
Hospitalized patient/test ratio change percentage	-18%	+23%	-15%	-39%	-34%	-33%	-33%	-33%

2C

	Triglycerides	Na^+	K^+	Cl^-	IL-6	LDH	Urine Culture	Blood Culture
January 10, to March 10, 2020	1,083	5,376	5,368	1,183	-	1,164	1,750	1,506
March 11, to May 11, 2020	594	3,160	3,131	940	14	1,360	730	848
Total test percentage changes	-45%	-42%	-41%	-21%	***	+17%	-58%	-44%
Outpatient admissions/test ratio change percentage	+49%	+60%	+59%	+116%	***	+218%	+13%	+53%
Hospitalized patient/test ratio change percentage	-36%	-32%	-32%	-8%	***	+35%	-52%	-35%

Number of tests performed in two periods between January 10, to March 10, 2020 and March 11, to May 10, 2020. Percentage changes in the number of tests between two two-month periods before and after pandemic, proportional test demand changes in outpatient clinics, proportional test demand changes in hospitalized patients. ALT (Alanine Aminotransferase), aPTT (Activated Partial Thromboplastin Time), AST (Aspartate Aminotransferase), CBC (Complete Blood Count), CK-MB (Creatinine Kinase MB), CRP (C-Reactive Protein), ESR (Erythrocyte Sedimentation Rate), LDH (Lactate Dehydrogenase), ProCT (Procalcitonin), PT (Prothrombin Time).

Table 3. Preanalytical error results in our clinical laboratory before and after pandemic in two-month periods.

	January 10, to March 10, 2020	March 11, to May10, 2020
Incorrect sample quantity	**0.01%**	**0.01%**
Hemolysis	**10%**	**8%**
Clotted sample	**0.4%**	**0.4%**
Inappropriate sample type	**0.07%**	**0.001%**

$$\text{Outpatient admissions/test ratio change percentage} = [100 - \frac{100 * \text{Total number of tests after pandemic beginning/outpatient admissions after pandemic beginning}}{\text{Total number of tests before pandemic beginning/outpatient admissions before pandemic beginning}}]$$

Figure 1A

$$\text{Hospitalized patients/test ratio change percentage} = [100 - \frac{100 * \text{Total number of tests after pandemic beginning/hospitalized patients after pandemic beginning}}{\text{Total number of tests before pandemic beginning/hospitalized patients before pandemic beginning}}]$$

Figure 1B

Figure 1A, 1B. Outpatient admissions and hospitalized patients test ratio change percentage calculations.

tine non-covid patient follow-up. This is because Covid-19 asymptomatic cases may have applied to the hospital with different comorbidities. This possibility naturally led physicians to demand more aggressive tests in Covid-19 follow-up, even if the patients are asymptomatic. In addition, possible false negativity of PCR tests, criticality of PCR timing and patient's disease time while taking the sample contributed to these phenomena. Again, when Table 2C was examined, the fact that the IL-6 test has not been previously studied can now be explained by this information.

When pre-analytical errors were examined, we realized that the results were quite good (Table 3). The new assignments that emerged with pandemic, possible panic mood, and the changeable shift system did not increase the preanalytical errors, and these were appreciated by health care professionals.

CONCLUSION

Some of the issues mentioned above required a different approach. Mobilized laboratories were not desired, but this may not apply to future pandemics. Although there was an increase in tests such as D-dimer and fibrinogen, a new test was not requested by physicians. However, if a new test request happens in the future, we, as the medical laboratory, should respond to the validation and verification of these new tests very quickly. Short turnaround time will be decisive in providing effective triage in emergencies. We should constantly follow the warnings of current health institutions and follow the on the job training. We must strive to protect not only physical but also psychological health of healthcare professionals. It is necessary to be prepared in the laboratory for structural change, budget change, equipment change, and most importantly, to anticipate issues.

Declaration of Interest:
None.

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