Original Article

Global Impact of the COVID-19 Pandemic on Cytopathology Practice: Results From an International Survey of Laboratories in 23 Countries

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BACKGROUND: To the authors' knowledge, the impact of the coronavirus disease 2019 (COVID-19) pandemic on cytopathology practices worldwide has not been investigated formally. In the current study, data from 41 respondents from 23 countries were reported. **METHODS:** Data regarding the activity of each cytopathology laboratory during 4 weeks of COVID-19 lockdown were collected and compared with those obtained during the corresponding period in 2019. The overall number and percentage of exfoliative and fine-needle aspiration cytology samples from each anatomic site were recorded. Differences in the malignancy and suspicious rates between the 2 periods were analyzed using a meta-analytical approach. **RESULTS:** Overall, the sample volume was lower compared with 2019 (104,319 samples vs 190,225 samples), with an average volume reduction of 45.3% (range, 0.1%-98.0%). The percentage of samples from the cervicovaginal tract, thyroid, and anorectal region was significantly reduced ($P < .05$). Conversely, the percentage of samples from the urinary tract, serous cavities, breast, lymph nodes, respiratory tract, salivary glands, central nervous system, gastrointestinal tract, pancreas, liver, and biliary tract increased ($P < .05$). An overall increase of 5.56% (95% CI, 3.77%-7.35%) in the malignancy rate in nongynecological samples during the COVID-19 pandemic was observed. When the suspicious category was included, the overall increase was 6.95% (95% CI, 4.63%-9.27%). **CONCLUSIONS:** The COVID-19 pandemic resulted in a drastic reduction in the total number of cytology specimens regardless of anatomic site or specimen type. The rate of malignancy increased, reflecting the prioritization of patients with cancer who were considered to be at high risk. Prospective monitoring of the effect of delays in access to health services during the lockdown period is warranted. ***Cancer Cytopathol* 2020;128:886-894**. © *2020 American Cancer Society*.

KEY WORDS: coronavirus disease 2019 (COVID-19); cytopathology; fine-needle aspiration; malignancy rate.

INTRODUCTION

During the recent coronavirus disease (COVID-19) pandemic outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] several national health organizations and different pathology scientific societies recommended reductions in routine health maintenance due to the health emergency, which also affected cytopathological practices around the world.[2-5] Normally, cytological specimens are obtained routinely regardless of whether the procedure is a screening procedure for more invasive histopathological examinations or a complete diagnostic, prognostic, and predictive evaluation. However, during the COVID-19 pandemic, procedures leading to a cytological sample needed to be carefully evaluated with respect to the risks and benefits to the patient as well as the health care provider. Indeed, to maintain the efficiency of health systems and to reduce the risk of infection for patients and medical staff, screening procedures were minimized or postponed until the "flattening of the curve" could be accomplished.[3,4] However, cytopathologists still were asked to ensure timely malignancy-related diagnoses because any delay could lead to an increase in cancer-related mortality.[6]

Clinical recommendations may be difficult to apply in routine practice, and to our knowledge it is unclear how these guidelines were implemented. The perception of reduced cytological activity during the COVID-19 pandemic has not yet been studied via real-world, practice-based evidence generated from different laboratories worldwide. Currently, the only available data have been reported by single institutions, and demonstrate a decrease in cytological workload.[7,8] It is interesting to note that, despite the reduced activity, the rate of malignant diagnoses significantly increased.[8] However, single-institution reports are not robust enough to draw reliable conclusions on a global scale or for assessment of the effect of the prioritization of cytological samples from patients considered to be at high risk of malignancy. Because the implementation of a nationwide network and registry of cytopathology diagnoses still is limited, worldwide data are difficult to gather without a collective effort. To fill this knowledge gap, a large number of cytopathologists from different countries reviewed their clinical reports to assess how cytological practices were impacted during the COVID-19 pandemic worldwide.

MATERIALS AND METHODS

Survey

Data regarding the activity of cytopathology laboratories were collected through an international survey.

An Excel questionnaire template was distributed through email to members of the CytoESP Working Group (cytopathologists from the European Society of Pathology) (https://www.esp-pathology.org/working-groups/esp-working-groups/cytopathology.html) and to cytopathologists who have taken part in 1 of the 9 Annual National Molecular Cytopathology meetings in Naples, Italy (https://www.molecularcytopathology.com/), accounting for a total of 65 invited participants. Only a single email and no reminders were sent. Participants were asked to provide data regarding their cytopathology

COVID-19 pandemic	n°
Total number of cytological samples	
Total number of exfoliative cytological samples	
number of different sample type	
i.e pap smear	
i.e urine	
i.e. serous fluids	
i.e.....	
i.e.....	
i.e.....	
Total number of aspirative cytological samples	
number of different sample site	
i.e breast	
i.e. lymph node	
i.e. thyroid	
i.e.....	
i.e.....	
i.e.....	
Distribution of the diagnostic classes in nongynecological samples	
Nondiagnostic	
Negative	
Atypical	
Suspicious	
Malignant	

Corresponding period, previous year	n°
Total number of cytological samples	
Total number of exfoliative cytological samples	
number of different sample type	
i.e pap smear	
i.e urine	
i.e. serous fluids	
i.e.....	
i.e.....	
i.e.....	
Total number of aspirative cytological samples	
number of different sample site	
i.e breast	
i.e. lymph node	
i.e. thyroid	
i.e.....	
i.e.....	
i.e.....	
Distribution of the diagnostic classes in nongynecological samples	
Nondiagnostic	
Negative	
Atypical	
Suspicious	
Malignant	

FIGURE 1. Survey questions. COVID-19 indicates coronavirus disease 2019.

practice during the first 4 weeks of the COVID-19 national lockdown.

The study period was individualized for each institution due to the variability of the lockdown among countries. In countries in which lockdown did not take place, cytopathologists were asked to provide data from the first 4 weeks of the peak infection spread. To assess changes, if any, in cytopathological practice, participants were asked to provide the same data compared with the corresponding period in 2019. Questions included in the survey are listed in Figure 1. Specifically, participants were asked to report on the total number of processed cytological samples, the total number of exfoliative samples specifying the number of different specimen types, the total number of fine-needle aspiration (FNA) samples specifying the different sampling sites, and the distribution of diagnostic classes in nongynecological samples (nondiagnostic, negative, atypical, suspicious, and malignant).

Statistical Analyses

All analyses were performed using the R statistical platform (version 4.0.2).

Differences between the 2 periods with respect to the ratio of exfoliative-to-FNA samples and to the malignancy rate were summarized using a meta-analytical approach, treating each institution as a different study. In the first analysis, the odds ratio (OR) was used as summary measure. The random effects model of DerSimonian and Laird was a priori selected due to the anticipated heterogeneity among institutions. Statistical heterogeneity between institutions was assessed using the I^2 statistic (ie, the percentage of total variability across institutions not due to sampling error). Standard thresholds were considered for the determination of I^2: ≤25% for low heterogeneity, 26% to 50% for moderate heterogeneity, and >50% for high heterogeneity. Results were shown using forest plots.

Global differences between the 2 periods with respect to the percentage of samples for each single anatomic site were assessed using the Fisher exact test and the corresponding *P* values were adjusted for multiplicity using the Benjamini-Hochberg correction procedure.

The ratio between exfoliative and FNA specimens and the sample site distribution were evaluated taking

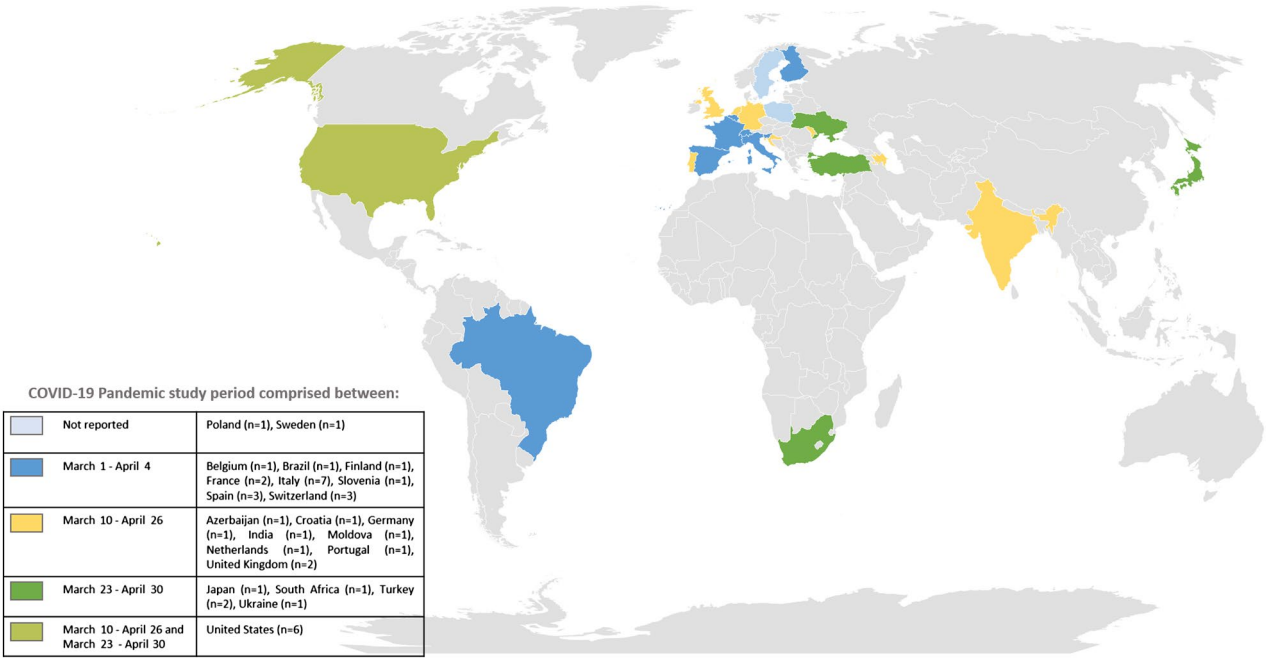

FIGURE 2. Countries represented by survey participants. COVID-19 indicates coronavirus disease 2019.

into account results from respondents who provided both exfoliative and FNA data (39 respondents). The sample site list was built considering sites provided from all participants; sites accounting for <30 samples in the reference period (2019) and sites reported as "other" all were grouped in the "other sites" category.

RESULTS

A total of 41 of 65 respondents (63%) from 23 countries worldwide (Azerbaijan [1 respondent], Belgium [1 respondent], Brazil [1 respondent], Croatia [1 respondent], Finland [1 respondent], France [2 respondents], Germany [1 respondent], India [1 respondent], Italy [7 respondents], Japan [1 respondent], Moldova [1 respondent], the Netherlands [1 respondent], Poland [1 respondent], Portugal [1 respondent], Slovenia [1 respondent], South Africa [1 respondent], Spain [3 respondents], Sweden [1 respondent], Switzerland [3 respondents], Turkey [2 respondents], Ukraine [1 respondent], the United Kingdom [2 respondents], and the United States [6 respondents]) joined the survey (Fig. 2). For the most part, data reflected single-institution activity (39 of 41 respondents; 95.1%), except in 2 instances (4.9%) in which multi-institutional data were provided, namely from the Pathological National Automated Archive (PALGA) Public Pathology Database of the Netherlands (https://www.palga.nl/en/public-pathology-database/) and from the National Health Laboratory Service of South Africa. Since the timing of COVID-19 lockdown differed among countries, as reported in Figure 2, each institution selected a 4-week time frame between March 1 and April 30, 2020, as the most significant health emergency period.

A total of 36 of the 41 respondents (87.8%) completed all required fields; in 2 instances (4.9%) only data relative to gynecological samples (Papanicolaou tests) were provided. With regard to the distribution of diagnostic classes, in 1 case (2.4%) suspicious and malignant diagnoses were merged; in another, only malignant diagnoses were reported; and, finally, in 1 case data were not reported.

Overall, data relative to 294,544 cytological samples, including 104,319 cytological specimens from the COVID-19 pandemic period and 190,225 cytological samples from the corresponding period in 2019, were provided, with an overall workload reduction of 45.3% (range, 0.1%-98.0%). Data for each single respondent are reported in Table 1. Data were anonymized and a number randomly was assigned to each respondent.

Because changes in cytological practice could modify the ratio between exfoliative versus FNA samples, a detailed analysis was performed; although the pooled analysis did not demonstrate a significant variation in the

TABLE 1. Total Number of Cytological Samples During 4 Weeks of the COVID-19 Pandemic Compared With the Corresponding Period in 2019 for Each Respondent

Respondent	COVID-19 Pandemic	Corresponding Period in 2019	Difference, %
1	440	1361	−67.7
2	164	622	−73.6
3	547	1001	−45.4
4	185	983	−81.2
5	1207	3402	−64.5
6	173	858	−79.8
7	50	475	−89.5
8	456	736	−38.0
9	273	1329	−79.5
10	436	2576	−83.1
11	292	2532	−88.5
12	289	495	−41.6
13	704	2856	−75.4
14	102	295	−65.4
15	120	143	−16.1
16	702	2784	−74.8
17	858	2366	−63.7
18	384	677	−43.3
19	526	3099	−83.0
20	87	353	−75.4
21	94	615	−84.7
22	2352	6214	−62.1
23	398	1237	−67.8
24	39	128	−69.5
25	162	806	−79.9
26	212	661	−67.9
27	190	962	−80.2
28	400	595	−32.8
29	248	828	−70.0
30	1615	1616	−0.1
31	3531	8658	−59.2
32	4	1783	−99.8
33	3479	12,680	−72.6
34	13,345	38,824	−65.6
35	456	508	−10.2
36	263	635	−58.6
37	126	1191	−89.4
38	10	500	−98.0
39	198	697	−71.6
40	68,429	79,116	−13.5
41	773	3361	−77.0
Total	104,319	190,558	−45.3

Abbreviations: COVID-19, coronavirus disease 2019.

ratio of exfoliative to FNA samples between the COVID-19 pandemic and the reference period (OR, 0.89; 95% CI, 0.74-1.08), a very high heterogeneity among the institutions was observed (I^2 of 95%) (Fig. 3).

For any single anatomic site, an absolute reduction in the total number of cases was observed consistently; this reduction was more evident (>50%) in samples from the cervicovaginal tract, urinary tract, breast, thyroid, salivary gland, soft tissue, anorectal region, and bone marrow, whereas it was less pronounced (<50%) in samples from 8 sites (serous cavities, lymph nodes, respiratory tract, central nervous system, gastrointestinal tract, pancreas, liver, and biliary tract); data are summarized in Table 2. Considering the contribution of any single anatomic site to the overall activity, significant decreases were observed in samples from the cervicovaginal tract, thyroid, anorectal region, and bone marrow ($P < .05$) during the COVID-19 pandemic compared with the corresponding period in 2019. Conversely, the percentage of samples from the urinary tract, serous cavities, breast, lymph nodes, respiratory tract, salivary gland, central nervous system, gastrointestinal tract, pancreas, liver, and biliary tract increased ($P < .05$). No significant variation in the percentage of soft-tissue samples was observed (Table 2).

With regard to the distribution of diagnostic classes in nongynecological samples, an overall increase of 5.56% (95% CI, 3.77%-7.35%) in the malignancy rate during the COVID-19 pandemic compared with the corresponding period in 2019 was observed (Fig. 4). When the suspicious category also was added to the malignant category, the overall increase was 6.95% (95% CI, 4.63%-9.27%) (Fig. 5). The heterogeneity among institutions was found to be very high in both analyses (I^2 of 81% and I^2 of 87%, respectively).

DISCUSSION

To our knowledge to date, the effect of COVID-19 on cytological practice has been documented by only a few reports reflecting single-institution experience.[7,8] The results of the current study demonstrated that the COVID-19 pandemic impacted cytology practices around the world by dramatically reducing the cytological specimen volume across specimen types by 45.3%. There are a number of explanations. First, screening programs were suspended or widely reduced according to recommendations issued by pathology scientific societies.[3,4] During the COVID-19 pandemic, the number of cervicovaginal tract samples obtained was dramatically reduced, both in absolute terms (−74.6%) and in proportion to the overall cytological sample volume (53.7% vs 68.61%; $P < .001$). Because it was recommended that cervical cancer screening activities be postponed rather than cancelled, future investigations once the health emergency is over are warranted to assess to what extent women have returned to cervical cancer screening programs.

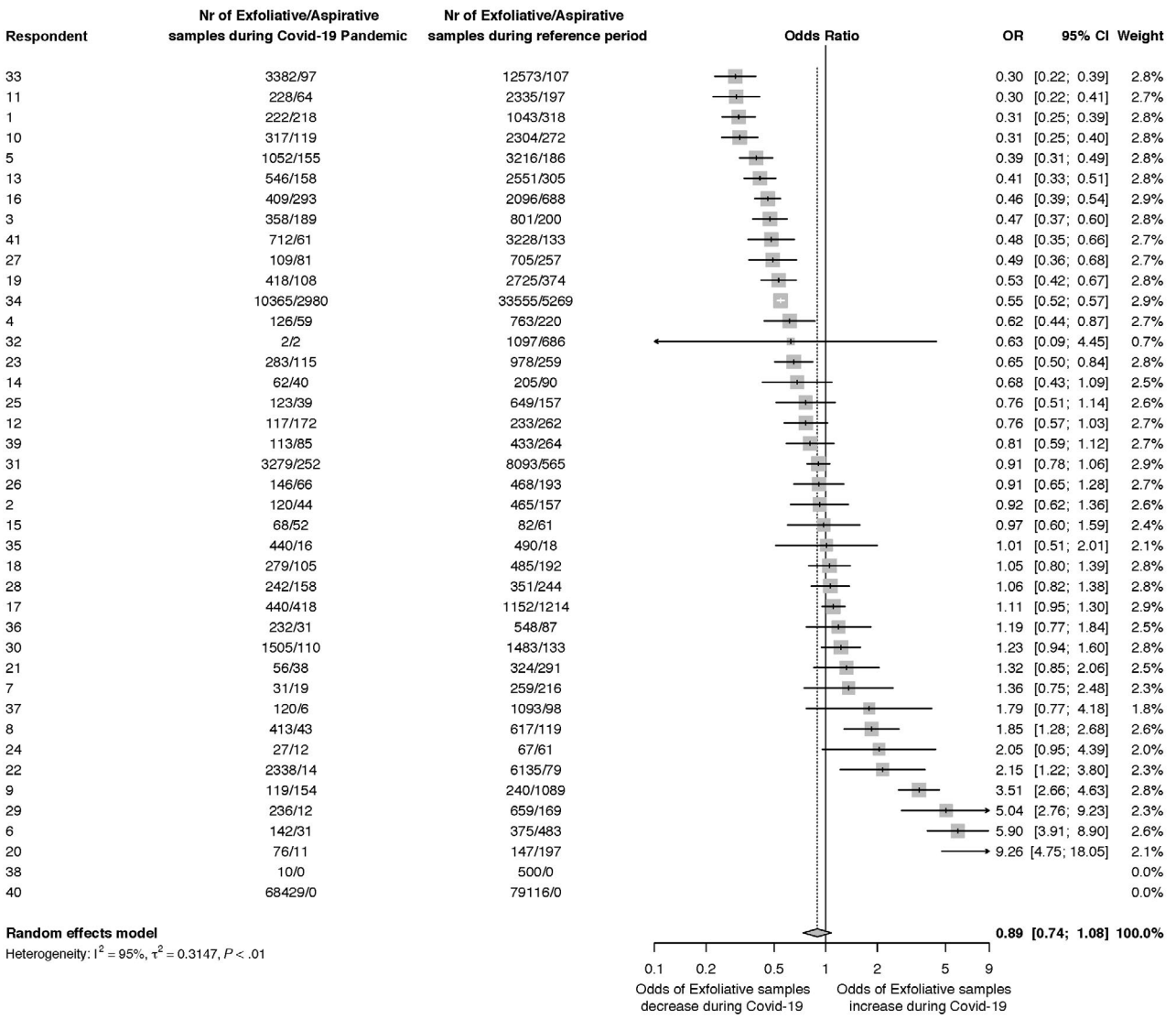

FIGURE 3. Meta-analysis forest plot demonstrating the differences between the coronavirus disease 2019 (COVID-19) pandemic and the corresponding period in 2019 (reference period) with respect to the ratio of exfoliative–to–fine-needle aspiration (FNA) samples. For each institution, the odds ratio (OR) between the exfoliative compared with the FNA samples observed during the COVID-19 pandemic and the reference period is shown. ORs with corresponding 95% CIs were graphically represented. ORs <1 indicate a reduction in the odds of exfoliative samples during the COVID-19 pandemic whereas ORs >1 demonstrate an increase in the exfoliative-to-FNA ratio during the COVID-19 pandemic. The pooled OR was obtained through a random effect model and is shown in bold. Nr indicates number.

Compared with the reduction in pap smears, the percentage of other exfoliative specimens, such as serous fluid, urine, and cerebrospinal fluid, demonstrated a significant increase, thereby explaining why there was no significant difference noted with regard to exfoliative versus FNA samples during the COVID-19 pandemic compared with the corresponding period in 2019.

A second explanation for the reduction in cytological samples lies in the fact that FNA specimens were limited to patients in whom a diagnosis rendered by the cytopathologist would immediately affect management. As an example, the current survey demonstrated an overall reduction in thyroid FNA samples both in absolute number (−78.9%) and, considering the overall cytological sample volume, in percentage (3.26% vs 5.02%; $P < .001$). It is interesting to note that the majority of asymptomatic thyroid nodules are not medically urgent[9,10]; in addition, most differentiated thyroid cancers have an indolent clinical course, thus explaining

TABLE 2. Overall Number and Percentage of Samples From Each Anatomic Site During the COVID-19 Pandemic and the Corresponding Period in 2019 (Global Volume Resulting From 39 Respondents Who Provided Both Exfoliative and FNA Data)

	Overall No.			Percentage		
Site	COVID-19 Pandemic	Corresponding Period in 2019	Difference, %	COVID-19 Pandemic, %	Corresponding Period in 2019, %	Adjusted *P*
Cervicovaginal tract	19,269	75,884	−74.6	53.7	68.61	<.001
Urinary tract	3778	8379	−54.9	10.53	7.58	<.001
Serous cavities	3101	4626	−33.0	8.64	4.18	<.001
Breast	980	2248	−56.4	2.73	2.03	<.001
Lymph node	2850	4651	−38.7	7.94	4.2	<.001
Thyroid	1169	5551	−78.9	3.26	5.02	<.001
Respiratory tract	2308 Exfoliative samples (n = 1892) (82%) FNA sample (n = 416) (18%)	4606 Exfoliative samples (n = 4007) (87%) FNA sample (n = 599) (13%)	−49.9	6.43	4.16	<.001
Salivary gland	195	482	−59.5	0.54	0.44	.021
Soft tissue	143	386	−63.0	0.4	0.35	.172
CNS	901	1309	−31.2	2.51	1.18	<.001
Gastrointestinal tract	81	161	−49.7	0.23	0.15	.005
Pancreas	378	518	−27.0	1.05	0.47	<.001
Liver	98	158	−38.0	0.27	0.14	<.001
Biliary tract	54	94	−42.6	0.15	0.08	.004
Anorectal region	6	183	−96.7	0.02	0.17	<.001
Bone marrow	41	220	−81.4	0.1	0.2	.003
Other sites	528	1153	−54.2	1.5	1.04	<.001
Total	35,880	110,609		100%	100%	

Abbreviations: CNS, central nervous system; COVID-19, coronavirus disease 2019; FNA, fine-needle aspiration.

the recommendation to postpone thyroid FNAs to the end of the health emergency, taking into account that a long and undefined "waiting time" between an endocrinologist's referral and performance of FNA generates anxiety for patients. Ideally, the decision to postpone the FNA should be taken by a multidisciplinary board, based on nodule location, ultrasound features, and clinical pathology laboratory data, in particular serum thyrotropin and calcitonin levels.[9,11] Dedicated guidelines, also addressing medicolegal issues, could be useful to assist the interventional cytopathologist in deciding to delay a thyroid FNA.

Compared with the reduction in thyroid FNAs, the overall reduction in cytology volume was less evident for specimens for which the rate of malignancy usually is higher. In fact, lymph node, respiratory tract, breast, and salivary gland specimens were reduced in absolute terms but, considering the overall cytological sample volume, their percentage was significantly increased compared with 2019. As an example, respiratory tract cytological specimens demonstrated a reduction of 49.9% but a relative increase in percentage compared with 2019 (6.43% vs 4.16%; $P < .001$). Moreover, respiratory tract FNA samples showed a slight relative increase (18% vs 13% in 2019) with respect to exfoliative specimens (82% vs 87% in 2019) (Table 2), suggesting a prioritization of FNA procedures that directly sample a suspicious lesion. The data from the current study indicate that, despite biosafety issues,[12-14] which are especially relevant in the handling of specimens from the upper and lower airways, lung cytopathology still was relatively robust during the health emergency. A more focused survey could shed light on how cytopathologists applied the recommendations to limit the practice of rapid on-site evaluation to avoid smears air-drying before Romanowsky staining[15] and to modify the alcohol content of liquid-based cytology collection medium.[16]

The overall data from the current study demonstrated a remarkable reduction in cytological workload across laboratory practices around the world, and also indicated that patients at high oncological risk were prioritized. The results also demonstrated an overall increase in the relative malignancy rate among nongynecological samples during the COVID-19 pandemic compared with the corresponding period in 2019 (+5.56%). This is even more evident

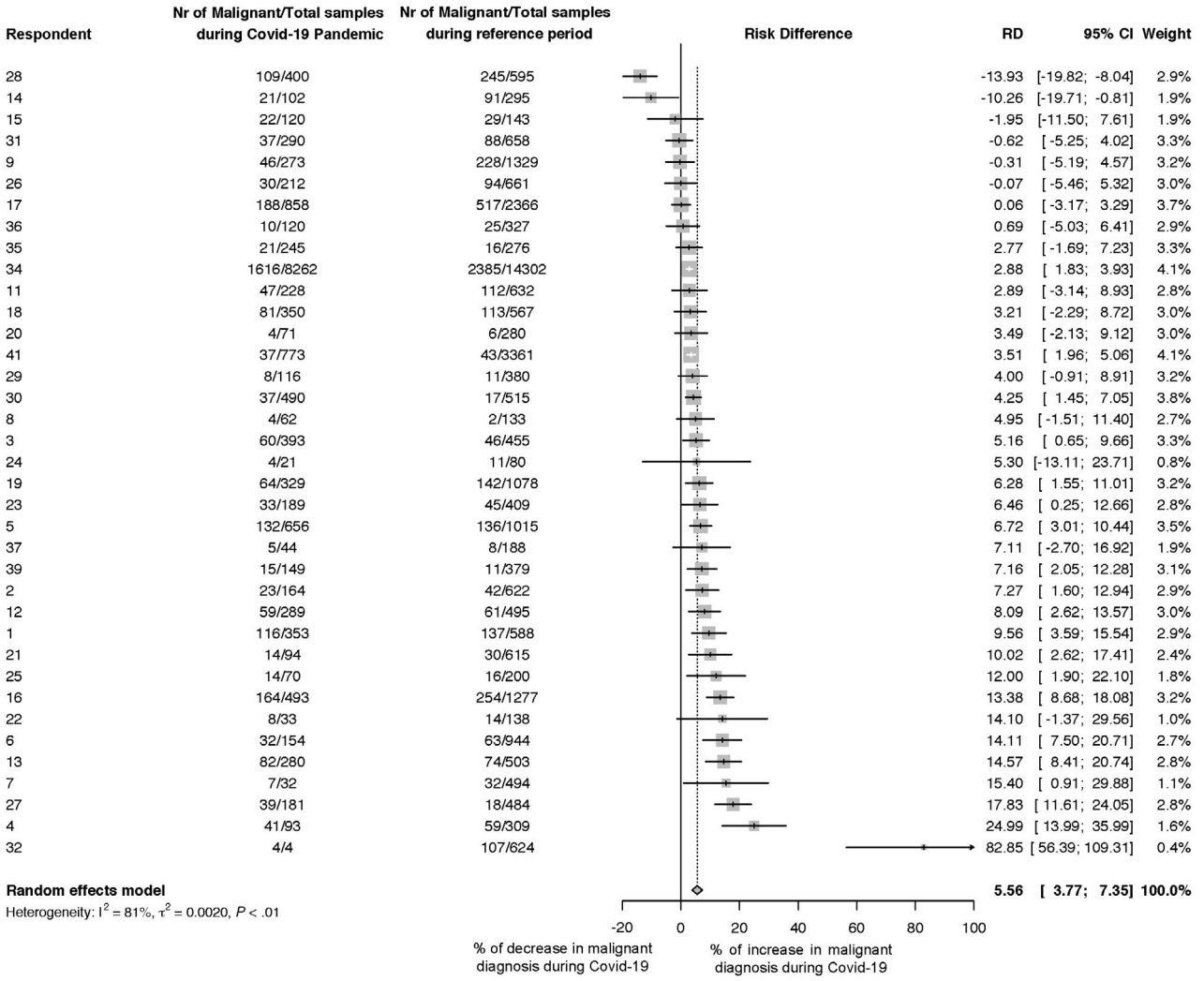

FIGURE 4. Meta-analysis forest plot demonstrating the difference between the coronavirus disease 2019 (COVID-19) pandemic and the corresponding period in 2019 (reference period) with respect to the malignancy rate. Participants who reported only data relative to gynecological samples (2 participants), did not report nongynecological diagnostic classes (1 participant), or who reported merged suspicious and malignant diagnoses (1 participant) were not included. For each institution, the malignancy rate observed during the COVID-19 pandemic and the reference period is shown. Rate differences (RDs) with corresponding 95% CIs were graphically represented. Negative RDs (RD <0) indicate a reduction in the malignancy rate during the COVID-19 pandemic whereas positive RDs (RD >0) represent an increase in the malignancy rate during the COVID-19 pandemic. The pooled RD was obtained through a random effect model and is shown in bold. Nr indicates number.

when the suspicious category also is taken into account (+6.95%), which is conceivable considering that the risk of malignancy of this category is not negligible, generally ranging from 50% to 100%.[17] The significance of this "relative" increase in the percentage of malignant and suspicious diagnoses should be investigated further, bearing in mind that the majority of laboratories had a dramatic decrease in the "absolute" volumes of many specimens.

Although the current study has provided robust data reflecting an international collective effort, several limitations should be highlighted. First, the study period was limited to 4 weeks between March 1 and April 30, 2020. This period of time does not necessarily correspond to the peak of the COVID-19 pandemic in countries still facing the health emergency at the time of this writing (eg, Brazil, India, and South Africa). Second, the data were analyzed globally, which may conceal differences among institutional practices. In this setting, further investigations may be warranted when also taking into consideration that certain continents are better represented

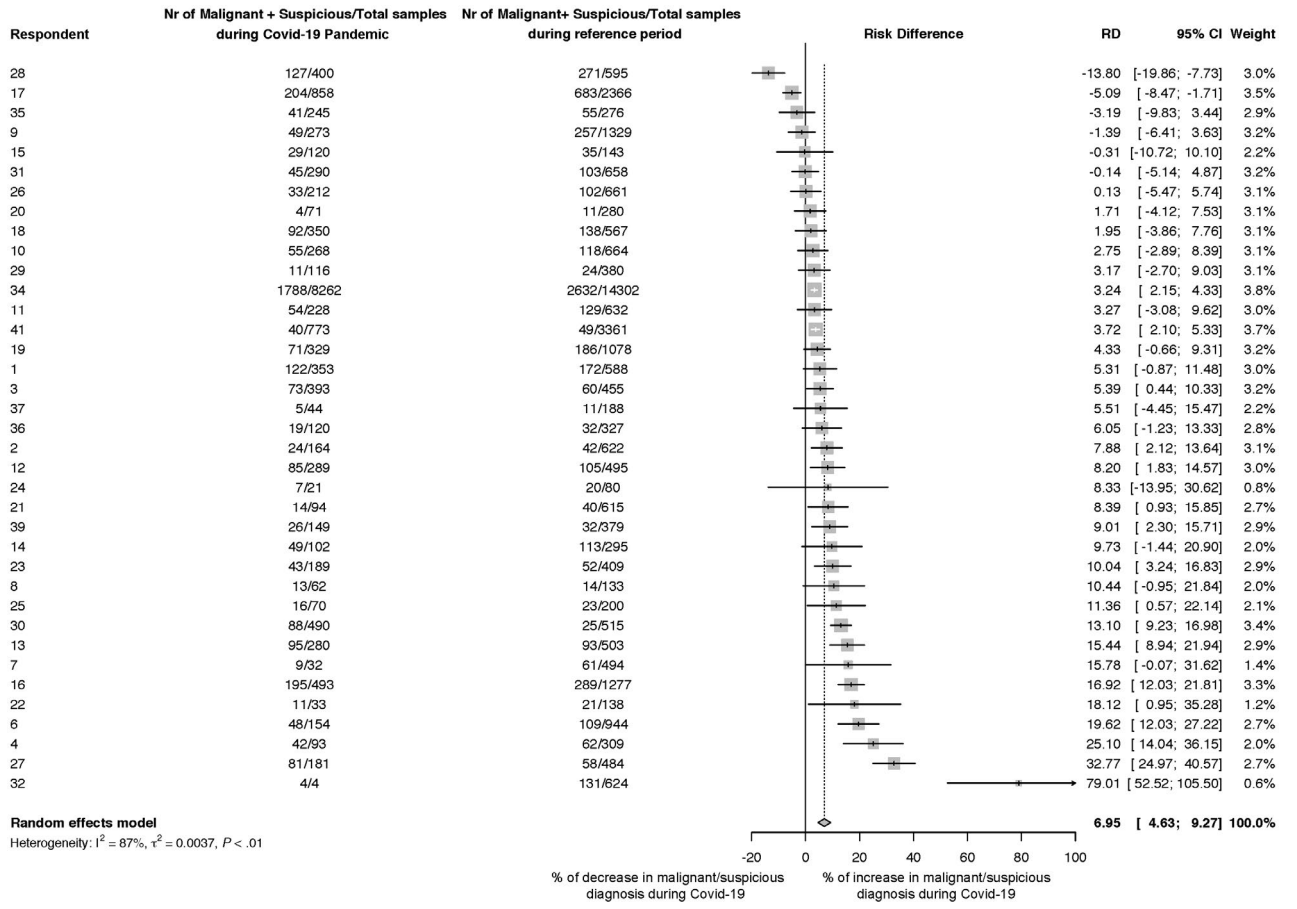

FIGURE 5. Meta-analysis forest plot demonstrating the difference between the coronavirus disease 2019 (COVID-19) pandemic and the corresponding period in 2019 (reference period) with respect to the malignancy and suspicious rates. Participants who reported only data relative to gynecological samples (2 participants), did not report nongynecological diagnostic classes (1 participant), or reported only malignant diagnoses (1 participant) were not included. For each institution, the malignancy and suspicious rates observed during the COVID-19 pandemic and reference period are shown. Rate differences (RDs) with corresponding 95% CIs are graphically represented. Negative RDs (RD <0) indicate a reduction in the malignancy and suspicious rates during the COVID-19 pandemic whereas positive RDs (RD >0) indicate an increase in the malignancy and suspicious rates during the COVID-19 pandemic. The pooled RD was obtained through a random effect model and is shown in bold. Nr indicates number.

than others and additional data from Asia and Oceania would make the survey more complete.

Conclusions

The COVID-19 pandemic dramatically impacted health systems and the activity of cytopathology laboratories worldwide. Laboratories universally experienced a dramatic reduction in overall cytological specimen volume across specimen types, which resulted in a higher malignancy rate overall. Although the increase in the percentage of malignant cases demonstrates the efficacy of prioritizing high-risk patients with cancer despite the pandemic, prospective monitoring of the effect of delays in access to health services during the COVID-19 pandemic warrants further investigation.

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CONFLICT OF INTEREST DISCLOSURES

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