INTRODUCTION

The spread of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) started in Wuhan (Hubei Province, People’s Republic of China) and led to the pandemic outbreak of coronavirus disease 2019 (COVID-19) at the start of 2020. This outbreak had an enormous impact on the healthcare services worldwide. The COVID-19 pandemic also affected medical laboratories. Haemostatic laboratories experienced a major rise in testing requests even though non-COVID, scheduled health care decreased. The reason for this rise in testing was the high activation of the immune system in patients with COVID-19 causing multiple coagulation abnormalities, such as

KEYWORDS

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disseminated intravascular coagulation and increased prevalence of pulmonary embolisms.\textsuperscript{5-9} Haemostatic parameters, including dramatically increased D-dimer and fibrinogen levels as well as prolonged prothrombin times, were marked as risk factors that indicate a prothrombotic state which is associated with severity of outcome and mortality.\textsuperscript{1,5,6,10-14} Therefore, ISTH guidelines recommend testing D-dimer levels, fibrinogen, platelet count and prothrombin time on admission.\textsuperscript{15,16} Altogether, this has led to an increase of 135\% in D-dimer test requests in one particular laboratory.\textsuperscript{4} The effect of these changes on the quality of testing performance is not known.

Despite treatment with a standard prophylactic dose of low molecular weight heparin (LMWH), approximately 30\% of the ICU patients still experienced a thrombotic event, including a venous thromboembolism event or a pulmonary embolism.\textsuperscript{6-8,15,17} These observations led to an intensified treatment with LMWH, which involves the use of a double dose of the regular concentration.\textsuperscript{8} This treatment regime needs regular monitoring of anti-factor Xa (anti-Xa) levels, which further increases the number of test requests in haemostatic laboratories.

The aim of the present study was to evaluate the impact of the COVID-19 pandemic on the quality of test output in haemostasis diagnostic laboratories. The impact on the performance was analysed by comparing relevant data from external quality assessment (EQA) surveys from 2019 to 2020 derived from the EQA programme of the ECAT Foundation. To evaluate the management of haemostasis laboratories, a national questionnaire was sent out to Dutch haemostasis laboratories to identify challenges and differences in management within the laboratories due to the COVID-19 pandemic. This overview may help haemostatic laboratories to gain more knowledge about the quality of test output and performance within different haemostatic laboratories and assist them in improving their strategy in response to changes caused by the COVID-19 pandemic.

2 \section{METHODS}

2.1 \section{Materials}

Survey response rates of ECAT data from both 2019 and 2020 were compared on the basis of various thrombosis and haemostasis parameters. To compare the quality of interlaboratory test output, similar samples were selected, derived from a survey in September/October 2019, March 2020 and December 2020. For the parameters factor VIII, antithrombin and protein C, a (borderline) normal coagulation control plasma was compared. For UFH and LMWH, a plasma with a level of approximately 0.6 IU/mL and 0.4 IU/mL was selected, respectively. For the APTT, PT and fibrinogen parameters, control plasma from a pool of anticoagulated patients (INR = 1.7) was used for the comparison.

Because the COVID-19 outbreak started in different countries in different periods, it was decided to look only in the Netherlands to find out in detail what effect the COVID-19 pandemic has on the performance of haemostasis laboratories. A web-based questionnaire was designed to evaluate the impact of the pandemic on the Dutch haemostasis laboratories. We evaluated the changes that took place in the logistics of the laboratory, the challenges that were faced with respect to measuring the coagulation parameters and whether the quality performance within the laboratory was compromised. The questionnaire was distributed to all haemostasis laboratories participating in the ECAT programme in the Netherlands. One submission per participating laboratory was allowed. The survey was available from 23 November 2020 to 1 January 2021.

Following the questionnaire, we looked in more detail at changes in assay request in four Dutch hospitals, by collecting the number of requested D-dimer, fibrinogen, factor VIII and anti-Xa tests in 2019 and 2020 per month. The data were collected from two peripheral hospitals and two academic hospitals, located in regions with different COVID-19 incidence.

2.2 \section{Statistical analysis}

In every survey, the interlaboratory coefficient of variation (CV) for methods including more than 10 participants was calculated for all participants worldwide. From these data, an overall mean and standard deviation (SD) of CV per sample and per parameter was calculated. Differences between the surveys were assessed by applying a one-way repeated-measure analysis of variance (ANOVA) using IBM SPSS statistics (version 25). p-Values less than 0.05 were considered to be statistically significant. In an additional calculation, the interlaboratory coefficient of variation was performed for the Dutch laboratories as well. For this smaller group methods were included with more than 5 participants except for D-dimer were the number of participants were 10 or more.

3 \section{RESULTS}

Laboratories participated with a similar response rate to the external quality programme during the COVID-19 pandemic as in 2019. A similar response was observed for each of the parameters (Figure 1). The response period was prolonged for 2 to 4 weeks at the start of the COVID-19 pandemic in March 2020 (depending on the survey), but only minimal changes in response rates were seen compared to 2019 (Figure 1A,B). The interlaboratory variation at the start of the COVID-19 period (the first survey in March 2020) was of the same order of magnitude for all parameters to that of comparable samples in 2019 (Table 1). Additionally, comparing a survey at the end of 2020 to the pre-COVID-19 period, also did not show differences in interlaboratory variation (Table 1). Also in comparison with samples from other surveys in 2019 compared to 2020, we did not find any differences in interlaboratory variation (data not shown). Furthermore, no difference was observed when comparing the interlaboratory variation of Dutch laboratories only (Supplementary table).
The questionnaire focused on four assays: D-dimer, fibrinogen (Clauss), anti-Xa activity assay and factor VIII activity. Of the 109 invited laboratories, 33 laboratories, who perform at least one of these tests, filled out the complete questionnaire. From these respondents, 97% measured D-dimer levels, 94% fibrinogen levels (Clauss), 61% anti-Xa activity and 39% factor VIII activity.

Many laboratories indicated that during the COVID-19 period, they had performed over 25% more anti-Xa activity (57%), D-dimer (55%) and fibrinogen (27%) tests than in the same period before COVID-19 (Figure 2). In this comparison, the number of requested factor VIII tests did not change for most respondents. When comparing the number of requests in October 2020 to October 2019, most laboratories observed an increase in the number of anti-Xa assays (76% of the respondents, increase: 5%-400%), in fibrinogen (58% of the respondents, increase: 25%-383%) and in D-dimer (88% of the respondents, increase: 5%-300%). The turnaround time of the tests in most laboratories remained unchanged for all tests. For 15% of the respondents, the turnaround time of the anti-Xa tests shortened in the COVID-19 period, due to increased frequency of the measurements or due to emergency diagnostics for dosage of LMWH/UFH. Furthermore, a prolonged turnaround time was observed for the D-dimer assay (10%), due to additional dilution steps necessary to measure the high values in plasma of COVID-19 patients. Most of the respondents did not report any problems with insufficient supplies of materials for the haemostasis tests. Only a small minority (6%) of the laboratories observed a delay in delivery time for supplies, such as diluent for the D-dimer test.

About half of the laboratories experienced a decrease in the presence of staff members. Six per cent of the laboratories increased their staff, due to the increased number of coagulation tests requests. Most respondents reported additional adjustment in their organization, such as working at home (72%), temporary stopping some tests (13%) or splitting the team (13%). The work pressure increased for more than 80% of the respondents due to, for example understaffing (42%), the increasing number of test requests (19%)
and more time-consuming activities, for example blood sampling of COVID-19 patients (23%). A large proportion of the respondents (71%) indicated an increase in absence due to illness.

Due to the increased test request and increased absence due to illness, it was expected that the work pressure increased during the second COVID-19 wave. Half of the respondents expected no difference in work pressure between the first and second COVID-19 wave. The other half of the respondents expected that the work pressure would further increase due to understaffing, or an increase in assay requests or both. Most respondents (78%) did not change the work strategy during the second COVID-19 wave. A minority of respondents planned to work with fixed personnel (6%) during the second wave, especially a specialized group of staff who would perform the COVID-19 patient sampling, or extra trained personnel (6%). The respondents confirmed that the COVID-19 epidemic did not affect the quality of tests performed. Only one respondent disagreed and cited the training of additional staff was as an explanation.

To further illustrate the differences in impact of COVID-19 on laboratories located in regions with a varying COVID-19 incidence, data of D-dimer, anti-Xa activity, fibrinogen and factor VIII activity assays performed were collected from four hospitals, and two peripheral (P) and two academic hospitals (A) located in different regions in the Netherlands with varying disease burden. A strong rise in anti-Xa activity assays was observed in all four hospitals during the first COVID-19 peak (Figure 3). However, for other assays, we saw a large variation between hospitals, for example a large increase in D-dimer assays performed was visible in the same period in two hospitals (hospitals 3 (A) and 4 (P)), while this did not occur in the hospitals located more to the north of the Netherlands (hospitals

|          | CV (%)                           | Mean ± SD Pre-COVID-19 | Mean ± SD COVID-19 (March 2020) | Mean ± SD COVID-19 (December 2020) | p value |
|----------|----------------------------------|------------------------|----------------------------------|------------------------------------|---------|
| APTT     | 3.9 ± 1.1                        | 4.4 ± 2.3              | 4.4 ± 2.1                        | n.s.                               |
| PT       | 4.5 ± 2.6                        | 3.9 ± 1.7              | 5.2 ± 4.3                        | n.s.                               |
| Fibrinogen| 6.8 ± 1.3                        | 8.1 ± 1.4              | 7.3 ± 1.1                        | n.s.                               |
| D-dimer  | 10.0 ± 3.0                       | 9.4 ± 2.3              | 10.4 ± 2.9                       | n.s.                               |
| Antithrombin| 5.0 ± 0.6                      | 4.5 ± 0.3              | 4.7 ± 0.9                        | n.s.                               |
| Protein C| 3.8 ± 0.5                        | 4.4 ± 0.9              | 4.0 ± 1.0                        | n.s.                               |
| Factor VIII| 8.1 ± 1.4                       | 10.5 ± 4.3             | 8.0 ± 1.6                        | n.s.                               |
| Anti-Xa (UFH)| 6.5 ± 1.5                      | 7.3 ± 3.9              | 6.4 ± 1.8                        | n.s.                               |
| Anti-Xa (LMWH)| 13.8 ± 4.2                   | 13.3 ± 5.0             | 13.5 ± 7.5                       | n.s.                               |

Note: Mean interlaboratory coefficient of variation (CV) of three similar samples derived from three different surveys are compared.

Abbreviations: SD, standard deviation per sample; n.s., not significant difference between pre-COVID-19 and COVID-19.
A peak in fibrinogen requests was only observed in hospital 3 (A) (April 2020: +162%, Supplementary data), while factor VIII requests dropped when the regular health care was suspended in April 2020 of 58% and 43% in the two academic hospitals (hospitals 1 (A) and 3 (A)) and normalized during the rest of the year (Supplementary data).
Our EQA data demonstrate that the COVID-19 pandemic did not compromise the overall quality of test performance in haemostasis diagnostic laboratories for the Dutch laboratories as well as worldwide. Respondents to the Dutch questionnaire confirmed the unchanged quality of test performance, despite the increase in workload. Furthermore, results from the questionnaire showed that during COVID-19, more than 25% increase in test requests for anti-Xa activity, D-dimer and fibrinogen levels was seen. This increase in combination with the logistical changes and absence due to illness led to an increase in work pressure in the majority of the responding laboratories.

We observed an increase in D-dimer, anti-Xa and fibrinogen after the start of the COVID-19 pandemic, and these observations are in line with observations of Ongen-Ipek and colleagues who reported an increase in D-dimer (136%) and fibrinogen (3.113%) assays in a single centre.4 Furthermore, the questionnaire showed the importance of increasing test material stocks, because some laboratories observed a delay in delivery time for supplies, such as diluent for the D-dimer test. There was a large variation in the number of tests performed and consequently in variation in the workload. The variation between laboratories was further illustrated by our data collected from four hospitals located in different regions of the Netherlands. As the COVID-19 infection was initially present in the south of the Netherlands, the number of hospital admissions of COVID-19 patients was the highest at the start of the epidemic in this part. Part of the variation between laboratories can be explained by the differences in disease incidence per region, which was illustrated by an increase in D-dimer assays performed in the high-incidence hospitals (Figure 4; hospital 3 (A) and 4(P)). However, this does not account for all interlaboratory differences. Further research will provide more insight into the origin of the variation between different laboratories within the Netherlands. Medication for hospitalized COVID-19 patients, such as remdesivir and dexamethasone, became available during the pandemic, and a higher dose of LMWH was administered to prevent thrombosis, shortening the time that patients hospitalized.18–21

In addition to the impact of COVID-19 on the performance of the assays, the impact on the management and the logistics within the laboratories was affected. Over 80% of the responding laboratories reported an increase in the absence of staff due to illness as a result of the COVID-19 pandemic. This increase might have been due to the illness of the personnel but could also have been due to COVID-19 safety rules, which require anyone to stay in quarantine if they have been in contact with a COVID-19 infected person or are suspected of having the COVID-19 infection.22 Another reason for the higher absence rate might be that the higher workload and extra time-consuming tasks led to an increase in work pressure.

While the workload increased for the treatment of COVID-19 patients, regular health care was reduced at the start of the COVID-19 pandemic.22,23 This was also seen in the number of factor VIII tests performed, which decreased in April 2020 in two haemophilia treatment centres. This decrease in testing was also observed in other diagnostic laboratories, for example in the pathology field.24–28 Thirteen per cent of the respondents to the questionnaire reported that they reduced their test panel to reduce workload.

As emphasized in previous literature, the impact on laboratories is an essential aspect that needs to be acknowledged. It was suggested that the daily activity of clinical laboratories may be affected by the large number of tests that have to be performed.3 Despite the increase in workload, haemostasis laboratories were still able to perform their EQA assessment for all scheduled surveys and no decrease in response rate was observed. Furthermore, the interlaboratory imprecision did not change after the COVID-19 pandemic started. This means that overall, the laboratories were able to preserve the quality of testing, despite all changes in test requests and logistic changes. The results of the questionnaire among Dutch haemostasis laboratories also confirmed that the COVID-19 epidemic did not affect the quality of tests performed.

The strength of this study is that the EQA data were derived from international haemostasis laboratories participating in the ECAT programme. A limitation is that evaluation of other effects such as the quantity performance of assays and logistical changes was limited to Dutch laboratories. Furthermore, only the overall changes in quality of test output are studied, and individual laboratory data are not compared.

In conclusion, the quality of testing performance of haemostasis laboratories internationally has not been affected by the impact of the COVID-19 pandemic, despite the increased workload. This increase in workload was caused by a major increase in work pressure and test requests, especially for D-dimer assays and anti-Xa activity tests, as observed in Dutch haemostasis laboratories.

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CONFLICT OF INTEREST
The authors have no competing interest.

AUTHOR CONTRIBUTIONS
RAA and MJH analysed data and wrote the original manuscript. MJH collected data for the quality of interlaboratory test output. RAA, NCV, MVL and SJL collected data of test requests from their hospital. MPMM and PM contributed expertise to interpret data. All authors reviewed the manuscript and have approved the final manuscript for publication.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

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