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CORRESPONDENCE

Pathology utilisation during COVID-19 outbreaks beyond viral testing: routine coagulation and D-dimer testing

To the Editor,

COVID-19 (Coronavirus Disease 2019) represents a well-recognised pandemic caused by infection with the virus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). At time of writing, over 410 million cases of COVID-19 have been reported worldwide, with nearly 6 million attributable deaths.¹ COVID-19 is a prothrombotic disorder that affects multiple haemostasis pathways, including both primary and secondary haemostasis.² In addition, platelets may also be affected and potential changes in platelet count can arise.³ Accordingly, a number of haematology tests may yield abnormal findings.⁴ Amongst these, D-dimer reflects an important test parameter, with levels not only being raised in COVID-19 but also related to disease severity, thus potentially having prognostic value.^{5,6}

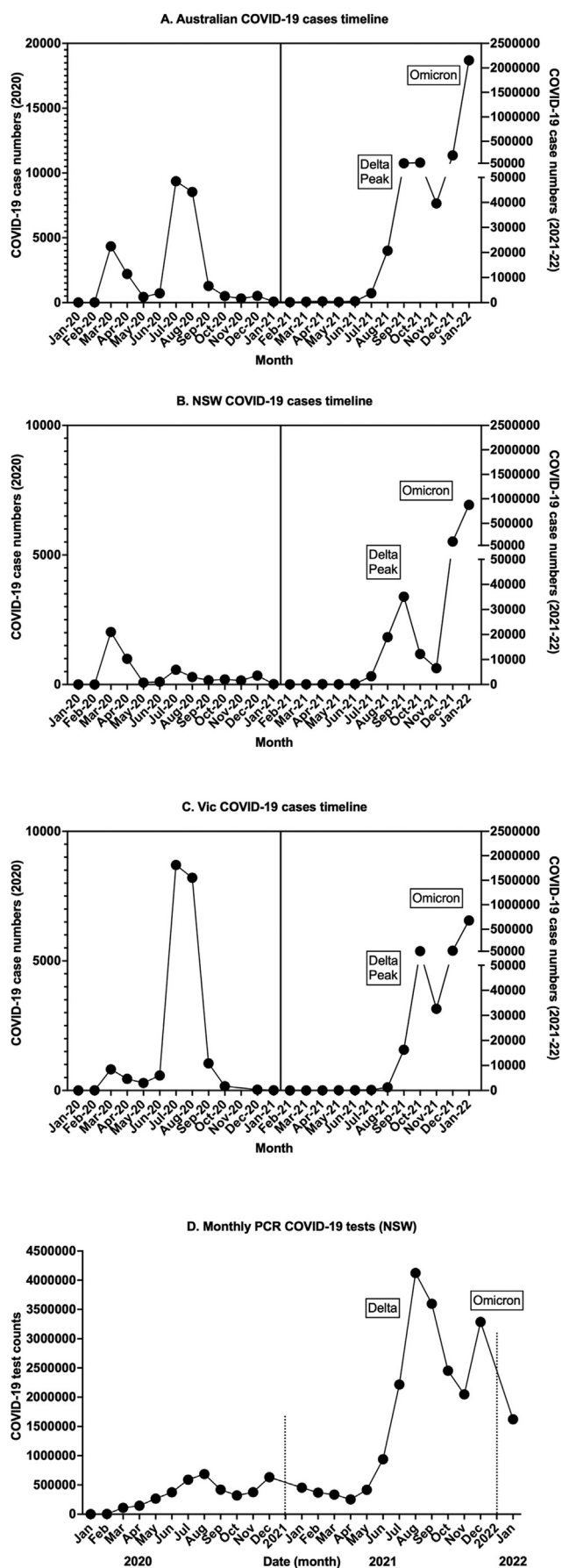
Australia had been relatively free of COVID-19 until recently. At time of writing, there have now been nearly 3 million reported COVID-19 cases, with over 4500 attributable deaths.¹ Of interest, there have been differing case numbers in different parts of Australia, essentially peaking during various COVID-19 'outbreaks'. The majority of cases have been reported in New South Wales (NSW; 1,197,969 cases; 1,713 attributable deaths), Victoria (976,256 cases; 2,284 attributable deaths), and Queensland (487,846 cases; 367 attributable deaths).¹

In this report, we highlight the effects of COVID-19, in particular 'outbreaks', on pathology utilisation, with a focus on coagulation testing, including D-dimer. We report that COVID-19 outbreaks are associated with changes in test ordering, in particular leading to very large increases in D-dimer testing. This report largely focuses on data from NSW, since these data are available to us, and links to data available from our pathology organisation, NSW Health Pathology, the largest public pathology group in Australia. Data on COVID-19 polymerase chain reaction (PCR) testing was obtained from NSW Health.⁷ Data on pathology testing statistics from NSW Health Pathology were extracted from the various pathology sites by various pathology Information Communication Technology (ICT) teams (see acknowledgements). Data are presented in synthesis, without any formal statistical analysis.

The number of reported Australian COVID-19 cases by month from 2020 is shown in Fig. 1A, with breakdowns for NSW and Vic shown separately in Fig. 1B,C. There

were a number of small outbreaks potentially identifiable in 2020 (left y-axis), but these were overshadowed by the 2021/2022 outbreaks (right y-axis), and essentially identifying four 'waves' of infection (Fig. 1A). Of interest, the second wave was predominantly seen in Victoria (Fig. 1C), and the third and fourth waves, respectively, reflecting the predominant Delta and Omicron variants, began in NSW (Fig. 1B) ahead of Victoria (Fig. 1C). Not only are the 2021/2022 outbreaks much larger, the vast majority of cases represented locally acquired infections with very few being acquired overseas or interstate, whereas for 2020 most cases were overseas acquired (data breakdown not shown). The COVID-19 case association with various local health districts (LHDs) also differed between outbreaks (data breakdown not shown). In 2020, the predominant LHDs were South Eastern Sydney and Northern Sydney, followed by Western Sydney and South Western Sydney. In 2021/2022, cases were predominantly from South Western Sydney and Western Sydney. Rural and Regional LHDs were largely spared from COVID-19 cases. The number of COVID-19 PCR tests performed in NSW by month in years 2020 and 2021/2022 is shown in Fig. 1D. The pattern also shows several peaks, somewhat analogous to COVID-19 cases in Fig. 1B. Note, however, that the demand for PCR testing in the latest (Omicron) outbreak overwhelmed the capacity of testing laboratories, and caused alternate uptake of rapid antigen tests (RAT). Thus, PCR test counts in the latest outbreak underestimate overall test numbers for COVID-19.

Testing statistics for the main routine coagulation tests performed at the ICPMR at Westmead Hospital is shown in Fig. 2A for the same 2020–2022 period. Coagulation profile means activated partial thromboplastin time (APTT) and prothrombin time/international normalised ratio (PT/INR), which represent the main ordered routine coagulation test 'panel'. Separate trends for APTT and PT/INR were similar (data not shown). Data for full blood count (FBC) are shown as an additional comparator. There seems to be a trend to reduction in testing for thrombin time over time; more interestingly, there was a notable increase in D-dimer testing, with several peaks also evident (Fig. 2A). Fibrinogen testing appeared to be falling in early 2020, but again shows two small peaks occurring coincident with the D-dimer peaks. There appeared to be little change in test numbers for FBC and coagulation profile. In general, we could also observe no major trends in any specialised haemostasis tests over the 2020–2022 period to date (data not shown), other than a noted increase in test requests for anti-platelet factor 4 (PF4) antibody testing, as related to investigation of vaccine induced thrombotic thrombocytopenia/thrombotic thrombocytopenia syndrome (VITT/TTS).

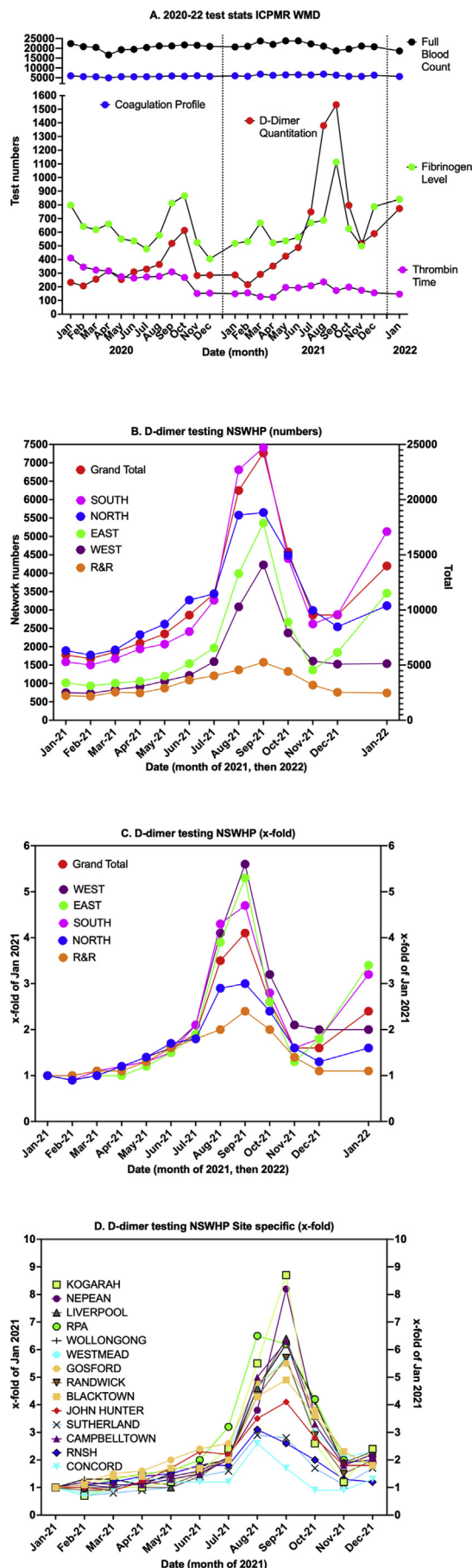


Nevertheless, the largest change was represented by the increase in D-dimer testing in late 2021, with a smaller peak emerging in January 2022. These peaks largely align to NSW COVID-19 case numbers (i.e., Delta and Omicron outbreaks). We further evaluated for changes in D-dimer testing across the entire network of NSW Health Pathology laboratories ($n=60$), and summary data are shown for 2021 in Fig. 2B,C, respectively, for total numbers of tests and x-fold increase over January 2021 test numbers. The clearly leading Network groups were, in order of test numbers, the South, North, East and West. However, in terms of x-fold increases, the leaders were West, East and South. Moreover, the trends clearly paralleled each other, and also followed the increase and subsidence of COVID-19 case numbers (Fig. 1B). Finally, the majority of D-dimer tests were primarily performed in the larger pathology testing sites, as associated with tertiary level teaching hospitals, and those most likely to carry the burden of COVID-19 admissions/hospitalisations. Incredibly, some individual sites increased D-dimer testing nearly nine-fold in September, as compared to January numbers (Fig. 2D).

To summarise, we report on COVID-19 related pathology test utilisation from the perspective of haemostasis and coagulation tests, and compared with data from NSW for COVID-19 associated cases (Fig. 1B) and COVID-19 tests (Fig. 1C), and using data from NSW Health Pathology. There was no appreciable impact on specialised haemostasis tests (data not shown), other than for anti-PF4 antibody requests, as associated with VITT/TTS, which is to be expected given the impact of VITT/TTS in Australia.^{8–10} For routine haematology tests, there was little change overall for FBCs and the routine coagulation tests APTT and PT/INR (Fig. 2A), although subtle changes could be hidden by the high baseline number of tests unrelated to COVID-19. There was a striking effect on D-dimer testing (Fig. 2), and to a lesser extent fibrinogen testing (Fig. 2A). We suspect that our experience can also be mirrored in other laboratory sites, in particular in NSW, Victoria and Queensland, which carried the greatest burden in COVID-19 case numbers in 2021.

D-dimer represents a breakdown product of fibrin, or clots, and so would be raised in patients with venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). COVID-19 represents a predominantly prothrombotic disorder, and many patients will potentially suffer VTE.¹¹ Indeed, in one meta-

Fig. 1 COVID-19 cases in Australia, NSW, and Victoria, and COVID-19 PCR tests in NSW, in 2020–2022.^{1,7} (A) Monthly case numbers for COVID-19 cases in Australia over the period of 2020–2022 inclusive (data to end of January 2022).¹ There were 2 peaks ('waves') of infection in 2020 (refer to left y-axis), and larger peaks (waves) in the later stage of 2021/start of 2022 (these representing the predominant Delta and Omicron outbreaks; refer to right y-axis). (B) Monthly case numbers for COVID-19 cases in NSW over the same period of 2020–2022.¹ (C) Monthly case numbers for COVID-19 cases in Victoria over the same period of 2020–2022.¹ Note that the second wave was predominant in Victoria, and that the third and fourth 'waves' started earlier in NSW than in Victoria. (D) Monthly PCR COVID-19 tests in NSW over the same period of 2020–2022.⁷ Note that the utilisation of PCR testing for the latest (Omicron) outbreak overwhelmed the capacity of testing laboratories, and caused alternate promotion of rapid antigen tests (RAT). Thus, PCR test counts in the latest outbreak likely underestimate overall testing for COVID-19.



analysis, the weighted mean prevalence (WMP) in COVID-19 patients of VTE was 31.3%, of DVT was 19.8%, and of PE was 18.9%.¹¹ In addition to VTE, or its risk, COVID-19 is also associated with pulmonary thrombosis, multi-organ micro-thrombosis, inflammation, and inhibition of fibrinolysis,^{2,5} all of which will potentially increase D-dimer levels and adversely impact COVID-19 patients. In turn, D-dimer is a potential prognostic marker for adverse outcome in COVID-19.^{5,6}

Accordingly, it should perhaps come as no surprise that D-dimer testing would increase in times of COVID-19 outbreaks, but the large increases in test requests have implications beyond that of workload. In regards to D-dimer testing, one additional potential issue is that of reagent supply. Given test numbers increased by up to nine-fold in some sites, similar increases in test reagent requirements were also evident. Thankfully, manufacturers were able to supply sufficient reagent for testing needs over this period, and thus this avoided the potential need for NSW Health Pathology to limit or suspend availability of testing. Nevertheless, NSW Health Pathology kept close watch over test numbers and supply chains to ensure continued availability of testing. Another potential issue is that of supply of other pathology consumables, as related to instrumentation, and also to blood collection. In particular, there is a worldwide shortage of blue cap citrate anticoagulant tubes,¹² as utilised for collecting coagulation and D-dimer samples. Accordingly, NSW Health Pathology kept close watch over collection tube supplies to ensure blood collections were also not limited or suspended.

In conclusion, our study speaks to the topic of pathology utilisation in COVID-19 beyond that of viral testing, in this case as related to coagulation/haemostasis testing. Our experience is likely mirrored by other laboratory sites, but probably represents the largest potential dataset available in Australia, given NSW Health Pathology is the largest public pathology organisation in Australia, and since D-dimer testing for COVID-19 would largely be performed in hospitalised patients at greatest risk of adverse outcomes. In addition, the state of NSW has suffered the highest burden of COVID-19 cases in Australia.

Fig. 2 Pathology test statistics in NSW Health Pathology related to routine coagulation tests, including D-dimer. (A) Test performance statistics for the ICPMR laboratory, Westmead Hospital, for the same time period of 2020–2022 inclusive (data to end of January, 2022). Coagulation tests means activated partial thromboplastin time (APTT) and prothrombin time/international normalised ratio (PT/INR), which did not appreciably change over time. There was a fall in thrombin time test requests, but more importantly several peaks in fibrinogen and D-dimer testing can be seen, in particular those peaks that align to the Delta wave in late 2021. Full blood count statistics, which also did not markedly change over time, are shown as an additional comparator. (B) Test performance statistics for D-dimer testing in NSW Health Pathology in 2021–2022 according to network location, and shown as test numbers. All networks recorded substantive increases in D-dimer testing, with least ‘growth’ in the rural and regional (R&R) network. (C) Test performance statistics for D-dimer testing in NSW Health Pathology in 2021–2022 according to network location, and shown as an x-fold increase compared to January numbers. All networks recorded substantive increases in D-dimer testing, with some networks increasing testing almost six-fold. (D) Test performance statistics for D-dimer testing in NSW Health Pathology in 2021–2022 according to specific location for larger metropolitan sites, and shown as an x-fold increase compared to January numbers. Some sites increased testing nine-fold.

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