Mini Review

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Reporting of D-dimer data in COVID-19: some confusion and potential for misinformation

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Abstract: Coronavirus disease 2019 (COVID-19) represents a new pandemic caused by severe acute respiratory syndrome virus coronavirus 2 (SARS-CoV-2). A previous pooled analysis clearly identified elevated D-dimer levels as being associated with severity of COVID-19. Since then, several other studies have provided clearer support for this initial evidence. However, potentially under-recognized by those reporting on D-dimer is the considerable variation in reporting units for D-dimer, and thus also the potential for misreporting of D-dimer data based on poor or incomplete reporting. A PubMed search was used to identify recent papers reporting on D-dimers in COVID-19-based studies. We report that: (1) most publications did not identify either the manufacturer or D-dimer product used; (2) most did not identify whether D-dimer values were reported as D-dimer units (DDU) or fibrinogen equivalent units (FEU) (~2× differences); (3) nearly half did not identify normal cut-off values; (4) some did not report numerical findings or units for D-dimer; (5) where reported, most identified units as either mg/L or μg/mL; (6) we identified at least four errors in reporting from 21 papers. It may not be possible to truly standardize D-dimer assays, but it should be feasible to harmonize D-dimer assays to a single unit of measurement.

Keywords: COVID-19; D-dimer; thrombosis; units.

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Introduction

Coronavirus disease 2019 (COVID-19) represents a new pandemic caused by severe acute respiratory syndrome virus coronavirus 2 (SARS-CoV-2) [1]. At the time of writing, there have been nearly 4 million confirmed cases of COVID-19, resulting in nearly 270,000 deaths [2]. Also, at the time of writing, there have been nearly 6000 papers published and listed on PubMed. These are incredible statistics for a disease that emerged late in 2019. The disease is characterized by a variety of pathophysiological derangements, including pulmonary inflammation and (micro)-thrombosis, that may also spill over into the systemic circulation [3–5]. The associated hyperinflammation and coagulopathy is in turn associated with a wide derangement in various hemostasis parameters, including D-dimer [6], prothrombin time (PT) [7], and thrombocytopenia [8, 9], with these also serving as potential prognostic markers of severe disease and/or mortality in COVID-19 [10].

D-dimers and COVID-19

In particular, a previous pooled analysis clearly identified elevated D-dimer levels as being associated with severity of COVID-19 [6]. At that time, the literature was still emerging, and it was recognized that an update would likely be required. Since then, several other studies meta-analyzed by Zhu et al. [11] and by Henry et al. [7] have provided clearer support for the initial evidence. Of key relevance, potentially under-recognized by those reporting on D-dimer is the considerable variation in reporting units for D-dimer [12], and thus also the potential for misreporting of D-dimer data based on poor or incomplete reporting. Although it is possible to identify at least 28 potential theoretical combinations of measuring units for D-dimer [12], a summary of the eight most common possibilities is provided in Table 1. Of additional interest here is that different D-dimer manufacturers preferentially report in several different units. There are actually two layers of potential misreporting here – the first reflects the reporting of D-dimer levels using either D-dimer

Table 1: Some examples of different units reported for D-dimer.

Normal cut-off values	DDU or FEU?[a]	Units	SI or conventional units	Examples of manufacturer kits reporting in these units	Manufacturer reported cut-off value[b]
0.25	DDU	mg/L	SI		
0.5	FEU	mg/L	SI[c]	Siemens Innovance® D-dimer	0.5 mg/L (VTE)
0.25	DDU	μg/mL	Conventional		
0.5	FEU	μg/mL	Conventional	Stago STA Liatest D-Di; Stago D-DI test; Roche Tina-quant D-Dimer; Roche Tina-quant D-Dimer Gen.2; Roche CARDIAC D-Dimer	0.5 μg/mL (VTE and NRR)
250	DDU	μg/L	SI		
500	FEU	μg/L	SI	Siemens Stratus® CS STAT Fluorometric Analyzer	552 μg/L (citrated plasma) and 682 μg/L FEU (lithium heparin plasma) (NRR); 450 μg/L (VTE)
250	DDU	ng/mL	Conventional	HemosIL D-Dimer HS	243 ng/mL (NRR) 230 ng/mL (VTE)
500	FEU	ng/mL	Conventional	HemosIL D-Dimer HS-500; Stago Asserachrom D-DI	500 ng/mL (VTE and NRR)
				HemosIL AcuStar D-Dimer	630 ng/mL (NRR) 500 ng/mL (VTE)
				Siemens Stratus® CS STAT Fluorometric Analyzer	552 ng/mL (citrated plasma); 682 ng/mL FEU (lithium heparin plasma) (NRR)
				Siemens IMMULITE®/IMMULITE 1000® Turbo D-Dimer and IMMULITE® 2000 D-Dimer	855 ng/mL (lithium heparin plasma) (NRR); 500 ng/mL (VTE)

[a]DDU, D-dimer units; FEU, fibrinogen equivalent units. [b]Cut-off values are sometimes identified as an upper limit of an NRR (normal reference range) and other times as the optimized cut-off for discrimination of venous thromboembolism (VTE; e.g. DVT, deep vein thrombosis). [c]SI unit is the recommended method of reporting clinical laboratory results, and also reflects the authors' recommendation, preferably in FEU. Other notes: (1) mg/L and μg/mL are equivalent units in terms of magnitude with cut-offs around 0.25 (DDU) or 0.50 (FEU). (2) μg/L and ng/mL are equivalent units in terms of magnitude with cut-offs around 250 (DDU) or 500 (FEU). (3) The main potential errors in D-dimer reporting can thus be represented by 'ignoring' DDU vs. FEU (=2-fold difference) or conversions from fractional numbers (e.g. mg/L or μg/mL) to larger whole numbers (e.g. ng/mL or μg/L; =1000-fold difference), for a composite potential of ~2000-fold differences. (4) Interestingly, different manufacturers appear to have different 'preferences' in regard to the units they use, and there are even differences within individual manufacturers. Such differences may relate to historical timelines of product development.

units (DDU) or fibrinogen equivalent units (FEU), which are approximately 2× those of DDU. The second layer reflects the actual measuring units used, which may be in ng, μg, mg, and even potentially g, and per mL, L, and potentially even μL. These second layer variations have the potential for some 1000-fold differences in reporting values (Table 1), that when combined with layer one leads to the potential for a 2000-fold error in reporting values.

Assessment of the current literature

To more fully appreciate the potential for issues to arise with poor or incomplete reporting of D-dimer data in the age of COVID-19, we undertook a simple PubMed search of 'COVID' and 'dimer' to identify recent papers reporting on D-dimers in COVID-19-based studies. We identified 31 such papers, and after excluding papers without new data (e.g. reviews, commentaries) as well as non-English language papers (all these being in Chinese) where we could not easily obtain the data, we were still left with nearly 20 papers reporting original data on D-dimer levels in COVID-19. All papers were published in 2020. The papers are listed in Table 2, together with a few other papers previously captured by us through alternate means [13–33]. Of major interest to us were the findings that: (1) most publications did not identify the manufacturer or D-dimer product that they used; (2) most publications did not identify whether D-dimer values were reported as DDU or FEU (~2× differences); (3) nearly half the publications did not identify the normal cut-off value; (4) some publications did not report numerical findings or units for D-dimer; (5) where reported, most publications identified units as either mg/L or μg/mL. Moreover, other known issues, such as age- and sex- related variance in normal and disease state [34, 35], as well as the high inter-method variation between methods (up to 42% for a single sample in one study [36]) are also generally ignored in such publications.

Table 2: Summary of reporting of D-dimers in COVID-19 from a recent literature search.

No.	Reference	Significant finding(s)	D-dimer method	FEU or DDU?	Cut-off	Units	Comments
1	Huang et al. [13]	41 Patients with COVID-19. 13 in ICU vs. 28 not in ICU. D-dimer level on admission was higher in ICU patients (median 2.4 mg/L [IQR: 0.6–14.4]) than in non-ICU patients (0.5 mg/L [0.3–0.8]) (p = 0.0042).	NR	NR	0.5	mg/L	Although not reported, appears to be FEU and also correct units.
2	Wang et al. [14]	138 Patients with COVID-19. 36 in ICU vs. 102 not in ICU. Higher levels of D-dimer in patients admitted to ICU (median 414 [IQR: 191–1324]) than not (203 [121–403]). Level of D-dimer was higher in non-survivors than in survivors.	NR	NR	**500**	**mg/L**	**Reported units must be in error. 1000× higher than expected. Common error not picked up in peer-review.**
3	Tang et al. [15]	183 Patients with COVID-19. 162 survivors vs. 21 non-survivors. Overall mortality was 11.5%; non-survivors had significantly higher D-dimer compared to survivors on admission (p < 0.05); 71.4% of non-survivors and 0.6% of survivors met the criteria of DIC during their hospital stay.	Stago	NR	0.5	μg/mL	Although not reported, appears to be FEU, and also correct units for Stago.
4	Zhang et al. [16]	138 Patients with COVID-19. 56 with severe disease vs. 82 with non-severe. Significantly higher levels of D-dimer, associated with severe patients (median 0.4 [IQR: 0.2–2.4]) compared to non-severe patients (0.2 [0.1–0.3]) (p < 0.001).	NR	NR	0.243	μg/mL	Although not reported, appears to be DDU, and also correct units.
5	Wu et al. [17]	201 Patients with COVID-19. Risk factors associated with the development of ARDS and progression from ARDS to death included higher D-dimer (HR, 1.02; 95% CI, 1.01–1.04). Higher D-dimer in ARDS (median 1.16 [IQR: 0.46–5.37)] than in non-ARDS (0.52 [0.33–0.93]) and in non-survivors (3.95 [1.15–10.96]) than in survivors (0.49 [0.31–1.38]).	NR	NR	NR	μg/mL	Units appear correct, but unclear if DDU or FEU, as no normal cut-off provided.
6	Zhou et al. [18]	191 Patients with COVID-19. 137 survivors vs. 54 non-survivors. Increasing odds of in-hospital death associated with D-dimer greater than 1 μg/mL (odds ratio, 18.42; 95% CI, 2.64–128.55; p = 0.0033) on admission. Higher D-dimers in non-survivors (median 5.2 [IQR: 1.5–21.1]) than in survivors (0.6 [0.3–1.0]) (p < 0.0001).	NR	NR	NR	μg/mL	Units appear correct, but unclear if DDU or FEU, as no normal cut-off provided. Probably FEU as survivor data also separated according to D-dimer values ≤0.5, >0.5 to ≤1, and >1.
7	Gao Y et al. [19]	43 Patients with COVID-19. 28 with mild vs. 15 with severe disease. Significant difference (p = 0.007) in D-dimer between severe (median 0.49 [IQR: 0.29, 0.91]) and mild (0.21 [0.19, 0.27]) groups.	NR	NR	NR	**μg/L**	**Reported units must be in error. 1000× lower than expected. Probably meant to be μg/mL. Common error not picked up in peer-review.**
8	Wan et al. [20]	135 Patients with COVID-19. 95 with mild vs. 40 with severe disease. Severe cases had higher plasma levels of D-dimer (median 0.6 [IQR: 0.4–1.1] vs. 0.3 [0.2–0.5]; p < 0.0001).	NR	NR	NR	mg/L	Units appear correct, but unclear if DDU or FEU, as no normal cut-off provided.
9	Zhang et al. [21]	95 Patients with COVID-19. Higher D-dimer level was related to severity of disease and composite endpoint (admission to ICU, mechanical ventilation, or death). Patients grouped into two according to highest D-dimer level during hospitalization. For ≤1 mg/L group, 9.5% of patients were severe cases, and 3.2% of patients reached the composite endpoint. For >1 mg/L group, 81.2% of the patients were severe cases, and 71.9% of the patients reached the composite endpoint.	NR	NR	NR	mg/L	Units appear correct, but unclear if DDU or FEU, as no normal cut-off provided.
10	Chen et al. [22]	274 Patients with COVID-19; 113 deceased and 161 recovered. D-dimer levels markedly higher in deceased patients (median 4.6 [IQR: 1.3–21.0]) than in recovered patients (0.6 [0.3–1.3]). 35% of 97 deceased patients and only 2% of 150 recovered patients had D-dimer concentrations above 21 μg/mL.	NR	NR	<0.5	μg/mL	Units appear correct; although not reported, appears to be FEU given the cut-off of 0.5.

Table 2 Continued

No.	Reference	Significant finding(s)	D-dimer method	FEU or DDU?	Cut-off	Units	Comments
11	Chen et al. [23]	21 Patients with COVID-19. 10 with moderate vs. 11 with severe disease. Severe cases had higher plasma levels of D-dimer (median 2.6 [IQR: 0.6–18.7)] vs. 0.3 [0.3–0.4]; p = 0.029).	NR	NR	<0.5	μg/mL	Units appear correct; although not reported, appears to be FEU given the cut-off of 0.5.
12	Tang et al. [24]	449 Patients with severe COVID-19. 99 received heparin (mainly LMWH) for 7 days or longer. 28-day mortality of heparin users was lower than that of nonusers in patients with an SIC score ≥4 or D-dimer >3.0 μg/mL.	Stago	NR	<0.5	μg/mL	Although not reported, appears to be FEU, and also correct units for Stago.
13	Qiu et al. [25]	36 Patients with COVID-19. 19 with moderate vs. 17 with mild disease. D-dimer significantly associated with severity of COVID-19 (mean [SD]: mild: 0.21 [0.18] vs. moderate: 0.36 [0.21]; p = 0.028).	NR	NR	<0.5	μg/mL	Units appear correct; although not reported, appears to be FEU given the cut-off of 0.5.
14	Guo et al. [26]	174 Patients with COVID-19. 37 with diabetes vs. 137 without. COVID-19 patients without other comorbidities but with diabetes (n = 24) were at higher risk of severe disease. D-dimer levels were significantly higher (p < 0.01) in diabetic patients (median 1.15 [IQR: 0.83–2.11]) compared with those without (0.54 [0.25–1.1]).	NR	NR	<0.5	**μg/L**	**Reported units must be in error. 1000× lower than expected. Probably meant to be μg/mL. Common error not picked up in peer-review.**
15	Zhou et al. [27]	Cohort of 17 patients with laboratory-confirmed COVID-2019, five with 'aggravated' disease. No difference in D-dimer values (non-aggravated: 0.29 ± 10.11 vs. aggravated: 0.28 ± 0.11; p = 0.922).	NR	NR	NR	mg/L	Units appear correct, but unclear if DDU or FEU, as no normal cut-off provided.
16	Mi et al. [28]	Data on 10 patients with a fracture and COVID-19. Nine of nine patients had a high **serum** level of D-dimer (1.622–17.2).	NR	FEU	<0.5	mg/L	Units appear correct, but concerning that authors report 'serum' levels of D-dimer.
17	Yin et al. [29]	28-Day mortality of heparin users was lower than that of nonusers in the COVID group with D-dimer >3.0 μg/mL (32.8% vs. 52.4%, p = 0.017). Patients with severe pneumonia induced by SARS-CoV-2 had a higher platelet count than those induced by non-SARS-CoV-2, and only the former with markedly elevated D-dimer may benefit from anticoagulant treatment.	Stago	NR	NR	μg/mL	Although not reported, appears to be FEU, and also correct units for Stago.
18	Li et al. [30]	25 Cases of COVID-19 who died. D-dimer rose in (9/12, 75%) patients with worsening conditions.	NR	NR	NR	NR	Limited information
19	Yuan et al. [31]	172 Patients with COVID after discharge; 25 still PCR positive after discharge: a significant inverse correlation existed between **serum** D-dimer level before discharging and the duration of treatment in these 25 patients (r = −0.637, p = 0.002), compared to the other 147 patients.	NR	NR	NR	NR	Limited information. Also concerning that authors report 'serum' levels of D-dimer.
20	Wang et al. [32]	Case series of COVID-19 patients. High D-dimer levels associated with worse disease. Case 1: >50,000 ng/mL; case 2: up to 40,490 ng/mL; case 3: 37,215 ng/mL.	NR	NR	NR	ng/mL	Limited information. Normal values for ng/mL are <250 (DDU) or <500 (FEU).
21	Liu et al. [33]	76 Patients with COVID-19. 30 with severe and 46 with mild disease. Higher D-dimer in those with severe (median 1 [IQR: 0.33, 2.42]) than mild (0.26 [0.16, 0.45]) disease (p < 0.001).	NR	NR	NR	**"μg"**	**Incorrect units. ?/mL. ?FEU/DDU?**

ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; DDU, D-dimer units; FEU, fibrinogen equivalent units; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; LMWH, low-molecular-weight heparin; NR, not reported; SD, standard deviation. In general, FEU = ~2 × DDU. Bold font = suggested errors in the literature.

Errors in the literature

Also important is that there are several errors in the reported values and/or units as reported in the literature related to COVID-19. For example, one of the earliest reports in this area of research by Wang et al., as published in JAMA [14], identified the units as mg/L, but also reported the cut-off as 500. Moreover, they reported values in COVID-19 patients as (median) 414 (interquartile range [IQR]: 191–1324) for those admitted to ICU vs. (203 [121–403]) for those not admitted to ICU. These numbers are about 1000× higher than those that would be expected in patients being tested for D-dimer using mg/L units, inclusive of the cut-off value. This is therefore likely to be an error, potentially due to conversion of µg/L to mg/L, possibly even because of a font or typographical issue ('µ' in symbol font is 'm' in normal text font). Incredibly, the authorship of Gao et al. [19] appears to have done the reverse, reporting units as µg/L, but then reporting numbers 1000× less than expected. In this case, the reported µg/L may potentially have been intended to be µg/mL. A similar error seems to have been made by Guo et al. [26]. Instead, the group of Liu et al. [33] reported units as µg, without any reference to volume; given the numbers they reported, this is likely to be µg/mL. Finally, several authors reported 'serum' D-dimers, and it is unclear if they really assessed serum as the sample type, or instead meant plasma D-dimers, as plasma is the generally accepted sample type. Naturally, you can measure D-dimer in serum, but the values detected will be different to those detected in plasma. First, plasma represents a 10% dilution of serum, so values would in theory be some 10% lower in plasma. On the other hand, the process of generating serum creates at least a theoretical possibility of entrapment of fibrin degradation products, including D-dimer, in the clot, and thus a potential for lower D-dimer values. In any case, no manufacturer to the best of our knowledge advocates serum as an acceptable sample for D-dimer testing, with citrate plasma (manufacturers marketing to hemostasis laboratories) or lithium heparin plasma (manufacturers marketing to chemistry laboratories) being the current options.

Irrespective, given most papers do not report the manufacturer or D-dimer product they used (and thereby information on the diagnostic performance of those tests is completely lacking), nor whether they used FEU or DDU, the translatability of any of this data for other laboratories or hospital centers may be completely lost. It is important to note that all the papers listed in Table 2 were

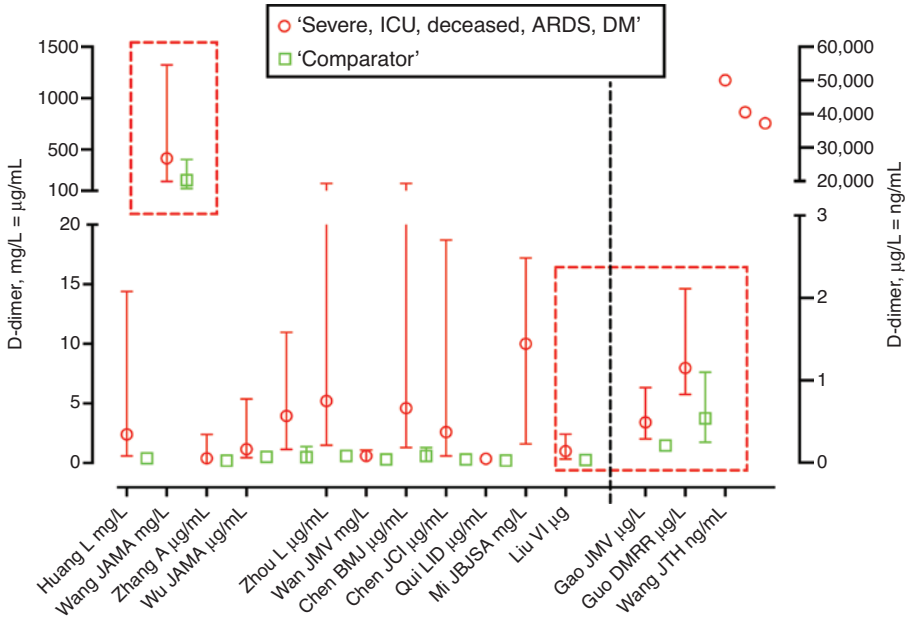
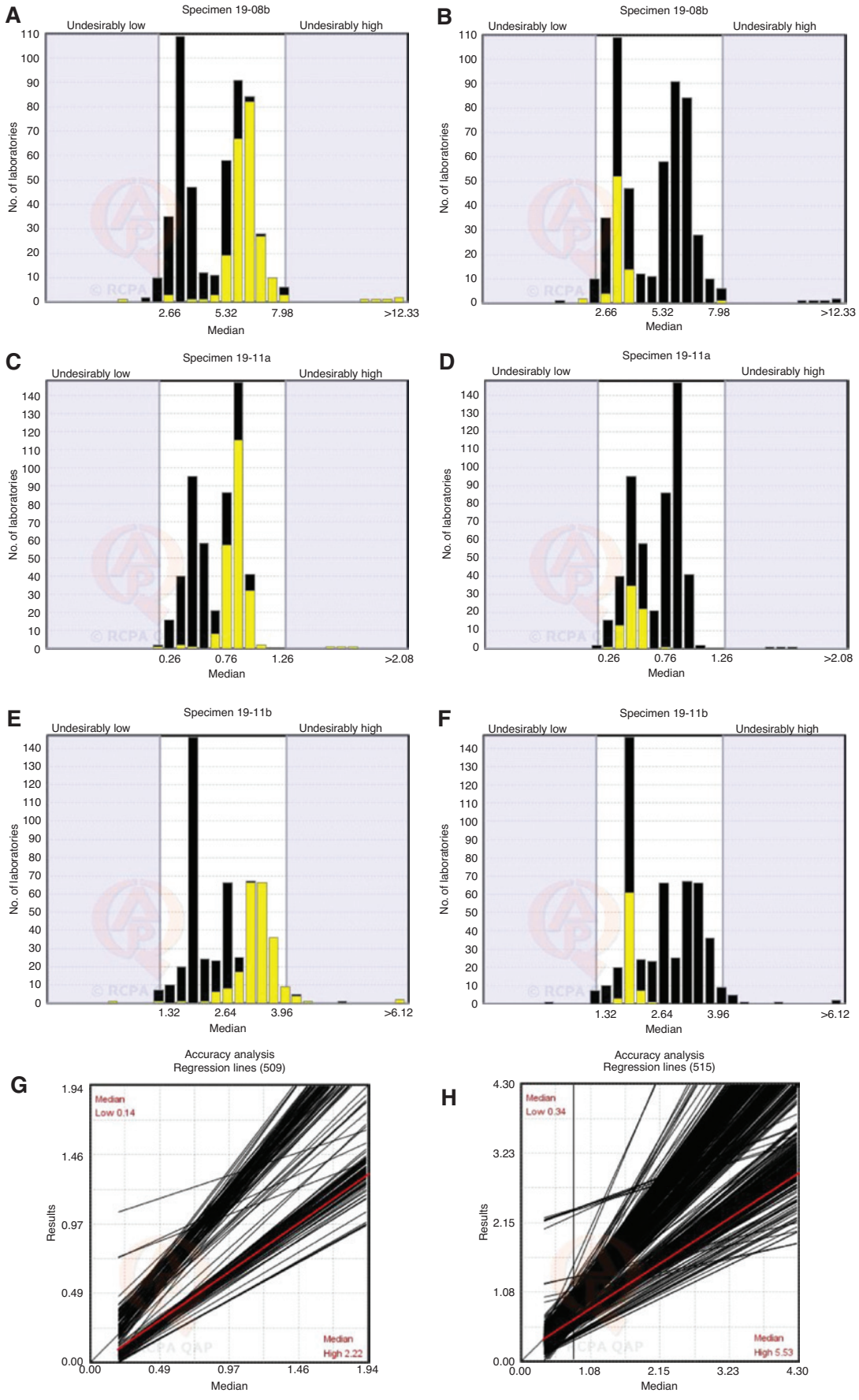


Figure 1: Plot of numerical data for D-dimer provided in publications identified in Table 2.
As per Table 1, mg/L and µg/mL are essentially equivalent units in terms of magnitude, and so data identified using these units are plotted against the left y-axis; alternatively, µg/L and ng/mL are equivalent units in terms of magnitude and data identified using these units are plotted against the right y-axis. The data sets in presumed error have been identified by the dashed boxes. The data published by Wang et al. [14] (left y-axis) appear to be some 1000× higher than expected. Conversely, the data published by Gao et al. [19] and Guo et al. [26] appear to be some 1000× lower than expected (right y-axis). Liu et al. [33] published data as 'µg' only, and is presumed to actually be µg/mL (left y-axis).


A
Specimen 19-08b
Undesirably low
Undesirably high
No. of laboratories
Median
2.66
5.32
7.98
>12.33
B
Specimen 19-08b
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2.66
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C
Specimen 19-11a
Undesirably low
Undesirably high
No. of laboratories
Median
0.26
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Median
1.32
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Accuracy analysis
Regression lines (509)
Median
Low 0.14
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High 2.22
Results
Median
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Accuracy analysis
Regression lines (515)
Median
Low 0.34
Median
High 5.53
Results
Median

Figure 2: Some recent examples of differences in reported D-dimer values using data from an external quality assessment (EQA) program (the RCPAQAP).
(A–F) Data summarizing reported values for participants of RCPAQAP for three recent test samples (18-08b, 19-11a, 19-11b) using either Siemens Innovance® D-dimer (A, C, E) or Diagnostica Stago Lia-test D-dimer (B, D, F) (as representing the two most used methods in this EQA program). Yellow bars represent the specific highlighted reagent, and black bars the remaining reagents. In general, data using the Siemens method is often higher than that using the Stago method. Although the two methods use different recommended reporting units (Table 1; respectively, mg/L and μg/mL), these should essentially reflect equivalent numerical values. Both methods also recommend use of FEU. Hence, the discrepancy remains to be explained; it may reflect different detection methods or perhaps some participants are reporting results in DDU? The spread of reported data for each reporting method also reflects on the inter-laboratory variation in test reporting, which for this EQA ranges from 3 to 15% as CVs (coefficient of variation) for within-method comparisons. (G, H) Linear regression lines for individual participants as reflecting the relationship between their lowest D-dimer to highest D-dimer reported values within either the 2018 (G) or 2019 (H) EQA cycles. There is an extraordinary variation in reported data for D-dimer testing of the same sample in different laboratories using different methods.

presumably peer-reviewed, and thus that there was even some failure of peer-review to identify the missing information, or the errors. Indeed, errors and omissions were far more likely to be reported in the non-thrombosis/hemostasis or non-laboratory medicine based literature. Where numerical data has been provided by the cited papers in Table 2, this has been shown in Figure 1 to further highlight the variance between publications. As shown, there are several papers presenting data that seems to be either ~1000× higher or ~1000× lower than expected, or as compared with the other papers. In addition, whilst most of the reported data is likely to be in FEU, this cannot be certain. As earlier noted, there is a high inter-method variation reported in the literature [36]. A more recent example of such inter-method variation is shown in Figure 2.

Recommended actions

We therefore once again call on all authors, all reviewers, and all journals, to ensure that publications reporting on D-dimers or identifying D-dimer values provide at a minimum, the manufacturer and kit used for D-dimer testing, whether DDU or FEU are reported, the assay cut-off value, and also the absolute measuring units (e.g. mg/L, ng/mL). Ideally, if relevant to the study population (e.g. venous embolism), the sensitivity, specificity, and negative and positive predictive values of D-dimer assays should also be quoted in addition to the normal reference ranges. Otherwise, most of the study data cannot be translated to any other laboratory or hospital, as it cannot be ascertained whether that laboratory or hospital is using the same D-dimer method.

It is well recognized by experts in the field that all D-dimer assays are not the same – they use different detection antibodies, different detection methods, and often different calibrators. In an earlier report [37], we identified that there were over 30 different D-dimer assays then commercially available, with these using over 20 different types of monoclonal antibodies. Indeed, the only similarity between some methods is the measuring units that are used, the cut-off value, and whether FEU or DDU are employed.

Unfortunately, most authors reporting D-dimer values in the literature, most reviewers reviewing this data, and most journals seem to wrongly assume that all D-dimer assays are the same. However, plasma contains a mixture of fibrin fragment complexes generated by plasmin acting on intravascular and extravascular clot-derived fibrin as well as circulating soluble fibrin [38]. Thus, D-dimer assays and individual patient factors lead to substantial variability in test results between kits. Moreover, different D-dimer assays vary in their specificity against degradation products. This is expected to generate several analytical problems because the specificity of monoclonal antibodies will differ markedly depending on the fibrin fragments used as the immunogen, and the assay calibrator [39]. In one study [40], plasma samples from patients with disseminated intravascular coagulation (DIC), deep vein thrombosis (DVT), and other clinical conditions, and those containing fibrinogen and fibrin derivatives, in addition to serial dilutions of pooled plasma samples, were distributed to 12 manufacturers of D-dimer assays. The correlation among the various assays was moderate, thereby identifying that D-dimer antigen is not homogeneous, and may be detected differently by different assays. High variability among assays was also reported at D-dimer values near the threshold for exclusion, when comparing results from 423 laboratories, with reports ranging from a lower normal range up to a 20-fold increased value [41].

Our review has also identified a failure in the peer-review process as related to COVID-19 and laboratory testing. Therefore, journals are also encouraged to request reviews of submissions from relevant societies or individuals with expertise in laboratory testing in order to vet the appropriateness of the submitted data.

Conclusions

It may not be possible to truly standardize D-dimer assays. There have been several attempts without success [37]. Nevertheless, it should be feasible to harmonize D-dimer assays to a single unit of measurement, and maybe one of the 'good' outcomes from COVID-19 pandemic will be the harmonization of D-dimer. We again call for renewed efforts to this end.

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