Standard Coagulation Tests in COVID-19

2

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2.1 Prothrombin Time (PT) and International Normalized Ratio (INR)

2.1.1 General Aspects

PT is one of the commonest coagulation tests. Its clinical use is basically to diagnose bleeding disorders, liver function, and effects of anticoagulants (warfarin). Technically, it is performed on platelet-poor plasma, adding calcium and thromboplastin (tissue factor, TF), and phospholipids, and measuring the coagulation time. Due to a high interlaboratory variability (basically due to differences in the nature and quantity of the activator), PT is generally associated to the INR (patient PT/mean normal PT according to the manufacturer of the test). From the pathophysiological point of view, the PT and INR explore the extrinsic pathway of coagulation, detecting disturbances of vitamin K-dependent coagulation factors (II, VII, IX, X, proteins C and S). Heparin usually does not prolong PT, unless in high doses. Other factors prolonging the PT are lipemia, hyperbilirubinemia, and dysfibrinogenemia.

2.1.2 Prolonged PT

Apart from the effects of oral anticoagulants, other clinical conditions may prolong the PT and increase the INR. Among these, acute or chronic liver failure with the consequent decrease in vitamin K-dependent coagulation factors is one of the most relevant.

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Disseminated intravascular coagulation (DIC) is a complex syndrome triggered by many different clinical conditions (trauma; central nervous system injuries; burns; various neoplasia; shock of different nature; infections; and others). Initiation of DIC is characterized by a thrombin burst (mainly triggered by tissue factor [TF] release) which activates platelets and fibrinogen. When the physiological inhibitors of thrombin generation (tissue factor pathway inhibitor; antithrombin) are overwhelmed, thrombin generation becomes pathological and DIC initiates. Uncontrolled clot formation triggers fibrinolysis, thrombocytopenia, and coagulation factor consumption. Therefore, on a clinical basis, and within the context of time progression, DIC may be characterized by thrombosis, bleeding, or both. Within this setting, a prolonged PT with thrombocytopenia, increased D-dimer levels, and decreased fibrinogen are diagnostic criteria.

Sepsis and septic shock are common triggers of this pattern. Early identification of coagulation derangement is of paramount importance in septic patients. In a series of 66 septic patients admitted to the intensive care unit (ICU), Liu and associates [1] found significantly higher INR values at the admission in the ICU in non-survivors, with an odds ratio of 2.0 for mortality in a multivariable model. A similar study, based on coagulation parameter in septic patients at the admission in the ICU [2], showed that prolonged PT values were associated with the development of acute kidney injury. In a retrospective study on 647 patients with sepsis or septic shock, Benediktsson and associates [3] could demonstrate that prolonged PT was associated with mortality, with a hazard ratio of 1.422. Overall, prolonged PT is a marker of severity and predictive for mortality in septic patients, likely anticipating the onset of a sepsis-related DIC.

2.1.3 Shortened PT

A shortened PT is associated with a number of clinical conditions characterized by a high risk for thrombotic complications, or overt thrombosis. These include diabetes, obesity, acute coronary syndrome, and stroke [4–6]. However, PT may be normal in a number of thrombophilic conditions, like congenital/acquired antithrombin deficiency, congenital/acquired protein C-S deficiency, factor V Leiden, and others.

2.1.4 PT in COVID-19

Despite the recognized pro-thrombotic pattern of COVID-19, PT is usually normal at least in the early phases of the disease [7, 8]. The first Chinese reports on COVID-19 patients are quite concordant in showing initially normal PT values with no difference between survivors and non-survivors [9–12]. However, two studies showed longer PT in patients with acute respiratory distress syndrome (ARDS) [9, 10], a finding not confirmed in another series [11]. A meta-analysis confirmed that in COVID-19 no clear changes of PT are evident, unless for a slightly prolonged value in more severe cases [13].

Pathologically prolonged PT and higher INR have been demonstrated in late stages of the disease, and are associated with the onset of a DIC pattern [14].

2.2 Activated Partial Thromboplastin Time (aPTT)

The aPTT measures the components of the intrinsic and common pathway of coagulation. The test is performed on plasma incubated with a reagent containing phospholipids and kaolin or ellagic acid. The time to clot formation is measured and compared with the reference value, producing a time (seconds) and an aPTT ratio.

The aPTT is sensitive to deficiency of the clotting factors II, V, VIII, IX, X, XI, and XII, and even to anti-factor VIII antibodies (in congenital or acquired hemophilia).

2.2.1 Prolonged aPTT

Congenital or acquired deficiencies of the above-listed coagulation factors prolong the aPTT. Hemophilia is one of the most common conditions. Lupus anticoagulant and antiphospholipid syndrome, even being pro-thrombotic conditions, prolong the aPTT acting on the reactant phospholipid component. Other clinical conditions leading to a prolonged aPTT are liver disease, decreased fibrinogen levels, and DIC. In septic patients, early prolongation of aPTT has been associated with bad outcomes [2, 3].

The main cause for a prolonged aPTT is unfractionated heparin (UFH) therapy, and aPTT can be used to monitor the anticoagulant effects of UFH (i.e., during extracorporeal membrane oxygenation). Conversely, the response of the aPTT to low-molecular-weight heparin (LMWH) and fondaparinux is variable and monitoring their effects requires titrated anti-FXa measure. aPTT is sensitive to the effects of dabigatran, but not in a dose-dependent fashion. Consequently, a normal aPTT makes unlikely the presence of high levels of dabigatran [15], but dabigatran monitoring requires specific tests (diluted thrombin time or ecarin time). Finally, aPTT is sensitive to intravenous direct inhibitors of thrombin, like bivalirudin and argatroban, and is commonly used to monitor the effects of these drugs.

2.2.2 Shortened aPTT

Differently from the PT, a shortened aPTT is considered a strong predictive marker for hypercoagulation [15]. Shortening of the aPTT is associated with a high level of coagulation factors (namely FVIII and fibrinogen) and is often found in the setting of an acute-phase reaction during inflammation and in sepsis. A short aPTT has been associated with deep venous thrombosis (DVT) [16] and arterial thrombosis [5].

2.2.3 aPTT and COVID-19

The first reports on COVID-19 patients from China offer a number of interesting data on aPTT that at first sight were probably underestimated. The aPTT has a tendency toward short values in a series of 99 cases, with 16% of the patients showing values shorter than the lower limit of normal range [10]. In a series of 201 COVID-19 patients [9], there was a trend ($P = 0.13$) toward shorter values in ARDS (26 s, interquartile range 22.5–35) than in non-ARDS (29.7 s, interquartile range 25.6–32.8) patients. Within ARDS patients, non-survivors had significantly ($P = 0.04$) shorter values (24.1 s, interquartile range 22.2–28.3) than survivors (29.6 s, interquartile range 24–35.7). This difference reached a *P*-value of 0.06 in a multivariable analysis. Finally, there was a trend ($P = 0.09$) toward shorter aPTT values in ICU patients in a series of 138 COVID-19 patients [11].

In a wide meta-analysis, no difference was found for aPTT values between severe and non-severe cases [13]. However, it should always be considered that some patients, and namely the most severe cases, could have been treated with UFH, which prolongs the aPTT. This is certainly a strong potential confounder.

2.3 Platelet Count

Platelet count and function are extensively treated in Chap. 6. Basically, the existing literature reports variable patterns ranging from thrombocytosis to normal platelet count to thrombocytopenia. The main player, in this setting, is likely to be the time course of the disease.

2.3.1 Thrombocytosis

Thrombocytosis in COVID-19 ARDS patients has been reported by some authors [12, 17–19]. In a series of 30 ICU patients followed for 14 days, Correa and associates [20] showed a progressive, significant increase of platelet count from admission to day 14. This behavior was more pronounced in less severe cases, with a median value of 469,000 cells/μL on day 14. Similar results were found in a study from our group [21], where viscoelastic tests demonstrated a platelet contribution to clot strength higher than the upper limit of normal range in 62% of the patients. There are different mechanisms that could induce thrombocytosis in COVID-19 patients [22]. Cytokine storm may be a major player, since various cytokines (IL-3, IL-6, IL-9, IL-11) can stimulate the production of megakaryocytes and IL-6 directly stimulates thrombopoiesis. The endothelial damage may induce a release of von Willebrand factor which may interact with megakaryocytes increasing platelet production. Finally, thrombopoietin production by the liver is directly stimulated by IL-6. The role of thrombocytosis in the determinism of thromboembolic events in COVID-19 patients is unclear, but it cannot be excluded. This introduces the

hypothesis that in the presence of thrombocytosis, specific antiplatelet therapies, and namely P2 Y_{12} inhibitors, may be useful [21, 22].

2.3.2 Thrombocytopenia

More focus exists on thrombocytopenia and its link to bad outcomes. There is in fact a consistent body of literature showing an association between thrombocytopenia, COVID-19 severity, and bad outcomes. In a meta-analysis including 1779 patients, Lippi and associates could find that platelet count was significantly lower in patients with severe patterns of COVID-19 and non-survivors [23]. The odds ratio for severe patterns of COVID-19 was 5.1 for patients with a low platelet count. Various studies showed a lower platelet count in non-survivors [2, 24–27]. However, other authors could not confirm this finding [9, 11, 28].

The mechanism(s) for thrombocytopenia in COVID-19 remain unclear. The cytokine storm could be involved in decreasing platelet synthesis; the development of autoantibodies could accelerate platelet destruction; finally, the injured endothelial layer may promote platelet activation, adhesion, and aggregation, and at the level of lung vasculature, megakaryocytes could be entrapped [22]. These last hypotheses, and namely platelet sequestration inside the newly formed thrombi, appear the most suggestive. Of notice, hemorrhagic complications in thrombocytopenic patients remain rare, and anticoagulation in this setting plays a confounding role.

2.4 Fibrinogen

2.4.1 General Aspects

Fibrinogen (coagulation factor I) is the most widely represented plasma protein coagulation factor. It is synthesized in liver hepatocytes and its plasma concentration range is 2.0–4.5 g/L [29].

Fibrinogen is a 340 kDa glycoprotein composed of two sets, each one containing three peptide chains: Aα, Bβ, and γ, linked by disulfide bridges [29, 30].

Together with platelets, fibrinogen and its derivate fibrin (FIa) are the components of a stable clot. However, fibrinogen has a double action in promoting clot formation.

The first is the development of a fibrin network: thrombin (FIIa) is the trigger of fibrinogen conversion to fibrin. Characteristics of thrombin generation are addressed in Chap. 4. Thrombin cleaves the fibrinopeptides A and B from the Aα and Bβ chains. Through this cleavage, fibrinogen is converted into fibrin monomers [31]. Subsequently, with the action of coagulation factor XIIIa (coagulation factor XIII activated by thrombin), the fibrin monomer is polymerized by a cross-link process based on reactions between two γ chains or one γ and one α chain [32]. The markers of fibrin formation are the fibrinopeptides A and B. The two principal fibrinogen

forms are high-molecular-weight (HMWF) and low-molecular-weight (LMWF) fibrinogen. HMWF promotes a fibrin network characterized by low-density thick fibers, while LMWF forms a high-density, thin-fiber fibrin network [33]. The first type of fibrin network is more efficient for angiogenesis and wound healing than the second.

The second very important role of fibrinogen is its ability to cross-link. Silent platelets may be activated through a number of different receptors and pathways; however, one of the most important activation pathways is again triggered by thrombin, which acts on the family of protease-activating receptors. Once activated, platelets express the integrin αIIb β3 (better known by clinicians as the GP IIb/IIIa receptor) on their surface. The GP IIb/IIIa receptor binds fibrinogen producing a cross-link between platelets (platelet aggregation).

Therefore, both these reactions see thrombin as the main player for fibrinogen contribution to clot formation; unless under very peculiar conditions (like a reptile bit injecting reptilase or botropase in the systemic circulation), without thrombin no conversion of fibrinogen to fibrin is elicited.

Fibrin network is destroyed by the fibrinolytic process that is addressed in Chap. 5.

Unlike for thrombin, where a number of drugs are available to directly or indirectly antagonize its action, controlling high levels of fibrinogen is a less common pharmacological intervention. Platelet aggregation through fibrinogen cross-link is blunted by GP IIb/IIIa inhibitors and this is commonly used in clinical practice. In the treatment of thrombotic complications, and namely pulmonary embolism and stroke, fibrinolytic (thrombolytic) drugs are commonly employed. A direct reduction of high levels of fibrinogen (hyperfibrinogenemia) is still outside the clinical practice.

2.4.2 Fibrinogen and Inflammation

The interaction between coagulation and inflammation is well known. The main player of this interaction is again thrombin generation elicited by blood-borne tissue factor (see Chap. 4). However, fibrinogen is another pivotal molecule, basically linked to inflammation by the complement system, through a common ancestral pathway [34].

Factor XIII is responsible for the generation of complement C5a during plasma clotting. Fibrinogen enhances the activity of the lectin complement pathway [35]. These (and other) mechanisms are inflammation triggers of coagulation. Inflammation, in turn, is able to not only trigger thrombin generation, but also elicit fibrinogen-dependent processes.

Fibrinogen synthesis is strongly enhanced by inflammation and fibrinogen is an acute-phase protein. Basically, the three genes producing the fibrinogen chains show an enhanced transcription in the early phases of inflammation. This is mainly triggered by elevated levels of interleukin-6 C-reactive protein [36].

2.4.3 Hyperfibrinogenemia

Hyperfibrinogenemia may result from genetic factors, but is more commonly associated with concomitant inflammatory diseases, sepsis, chronic kidney disease, lifestyle (smoking), and other physiological conditions (pregnancy, acute exercise). Elderly subjects and females have higher fibrinogen values [37]; seasonal variations are reported [38].

Increased fibrinogen levels are associated with an increased cardiovascular risk. Many studies demonstrated an association between elevated plasma fibrinogen levels and cardiovascular risk [39–41]. Even venous thromboembolism is associated with high fibrinogen levels. Therapies targeted to reduce the cardiovascular risk, like ACE inhibitors, result in a reduction of fibrinogen levels. However, it is not totally demonstrated that the link between high fibrinogen levels and cardiovascular events is causative rather than associative. Conceptually, elevated fibrinogen levels could trigger cardiovascular events (acute myocardial infarction, stroke, mesenteric infarction …) through a number of pathways. These mainly pertain the role of fibrinogen in the context of an unstable arterial plaque. Within this context, fibrinogen may certainly contribute to thrombus formation. In animal models, high fibrinogen levels shorten the time to vessel occlusion, generating a thick, stable, and lysis-resistant clot. Even in case of stable, chronic atherosclerosis plaques contain fibrin deposit that contributes to plaque growth and possible evolution to instability [33].

However, as already mentioned, the type of fibrinogen incorporated in the clot determines different degrees of firmness and resistance to lysis. Basically, clots characterized by an increased fibrin fiber density (produced by LMWF) are more likely to be associated with cardiovascular events, as demonstrated in young subjects with acute coronary syndrome [33].

2.4.4 Fibrinogen and COVID-19

High levels of fibrinogen are almost invariably reported in patients with COVID-19, both in less or more severe cases [20, 21, 42–48]. Values in the range of 6–7 g/L are not unusual. With respect to the time course and the role of anticoagulation, data in literature are concordant.

In critically ill patients aggressively treated with steroids and anticoagulation, there is a significant progressive decrease of fibrinogen levels [20, 21]; however, no differences were found between patients receiving low- and high-dose anticoagulation [44].

Discordant reports exist with respect to the severity of the disease and the presence of thrombotic complications. Fibrinogen levels have been found higher in patients with thrombotic complications in some studies [46] but not in others [47]. In a large series of patients, Li and associates demonstrated significantly lower fibrinogen levels in patients with venous thromboembolism vs. patients without

[49]. The severity of the disease is associated with higher levels of fibrinogen in some studies [42, 45, 46], but others could not confirm this finding [20, 50, 51].

Interestingly, the inflammatory trigger for fibrinogen formation was clearly highlighted in a study from our group, where a significant association between IL-6 values and fibrinogen levels was found (Fig. 2.1) [21].

The link between fibrinogen levels and outcome in COVID-19 patients reflects the same uncertainties of the link between fibrinogen levels and cardiovascular events. In a nice overview of this issue, Thachil introduced the concept of the potential protective role of fibrinogen in the setting of infective diseases [52]. In the presence of a microbial aggression, fibrinogen acts as an acute-phase protein targeted to defend the host. Fibrinogen is a ligand of leukocyte integrin regulating the inflammatory response; additionally, thrombus formation itself may limit the spread of the invading pathogens, mainly at the level of lungs. The author hypothesizes a multiple-step mechanism for hyperfibrinogenemia in COVID-19 patients. At the initial stage, the main role is to limit the exaggerated inflammatory reaction, and this could be a beneficial effect. Lately, thrombus formation becomes predominant, occurring at a low level, and with moderately increased D-dimer. Finally, massive thrombus formation induces a reduction in fibrinogen levels, with a concomitant increase in D-dimer. According to this theory, the ratio between fibrinogen and D-dimer could be more suggestive of the time course of the disease and of its progression toward severe patterns. In the final stage, low levels of fibrinogen (and platelets) create the environment for hemorrhagic complications.

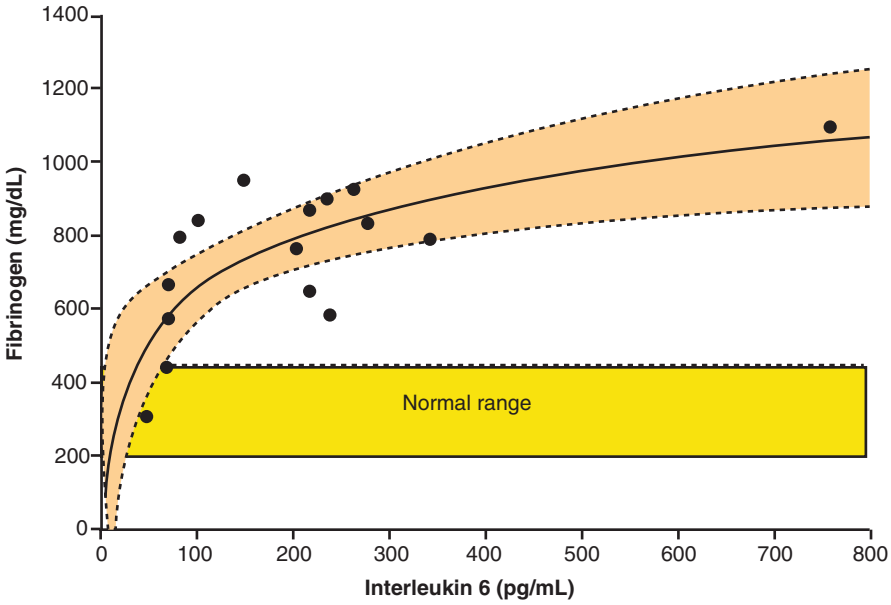

Fig. 2.1 Association between IL-6 and fibrinogen levels. Data from Ref. [21]

2.5 D-Dimer

2.5.1 General Aspects

D-dimer is a term defining multiple peptide fragments derived from plasmin degradation of fibrin polymer. Plasmin cleaves fibrin polymer at specific sites, producing fibrin degradation products (FDP) that, in this first step, are large [53]. Subsequently, the breakdown process generates the fragment D-dimer/fragment E complex (DD/E complex) that is a small (228 kDa) compound [53]. The DD/E is not the only degradation product included in the definition of D-dimer, which includes larger (over 10,000 kDa) FDP [54]. Small amounts of D-dimer are detectable in healthy subjects and derive from the spontaneous conversion of fibrinogen into fibrin and the consequent low-degree fibrinolysis.

Fibrinolysis is extensively treated in Chap. 5. For the purposes of the present sub-chapter, it is worthwhile to highlight that the products derived from fibrinogenolysis and fibrinolysis (both in the domain of FDP) are different. Only stable fibrin polymers, obtained through the action of FXIII, will produce D-dimer once plasmin activates their degradation. Monoclonal antibodies of the currently available immunoassays do not detect other FDP and are specific for D-dimer [55].

There are various factors that may affect a laboratory measure of D-dimer. Preanalytical variables include the size and length of the needle; the tube material; and the amount and quality of anticoagulant (recommended: sodium citrate; allowed: heparin, EDTA). The great majority of the assays use plasma, but whole-blood tests are available.

There are two units of measure for D-dimer: the FEU and the DDU. The FEU compares the mass of D-dimer to that of fibrinogen and the DDU determines the mass of the estimated weight of D-dimer [53]. The conversion factor between FEU and DDU is 2 (FEU=DDU × 2). Regardless of this, the final measure units are expressed in ng/mL, mg/L, μg/mL, and others. So, there are more than ten combinations of D-dimer measure depending on FEU vs. DDU and on the final measure unit. This is certainly a challenging condition for clinicians, and clinical laboratories should be very active in communicating to the clinicians any change in analytical practice, unit of measure, and normal range.

From this perspective there is a conventional cutoff at 500 μg/L FEU (250 μg/L DDU) [53–55], but the clinicians should be aware that age is a strong physiological determinant of D-dimer production, and that age-adjusted cutoffs are logical. A simple age-adjusted cutoff value (FEU) is age (years) × 10 [53].

The clinical applications of D-dimer measure belong to the scenarios directly or indirectly related to thrombogenesis and fibrinolysis. These include cerebral venous thrombosis, acute aortic dissection, acute mesenteric ischemia, venous thromboembolism (namely, pulmonary embolism), and DIC. Diagnostic use of D-dimer in the setting of venous thromboembolism has been widely addressed. D-dimer measure is a highly nonspecific test, since D-dimer values increase for

Table 2.1 Principal clinical conditions leading to increased D-dimer

Physiological and paraphysiological
Gender male
Advanced age
Neonatal period
Pregnancy/puerperium
Poor mobility
Prolonged hospitalization
Chronic diseases
Chronic inflammation
Atrial fibrillation (with left atrium thrombi)
Cancer
Heart failure
Ischemic cardiopathy
Liver disease
Renal disease
Aortic aneurysm
Deep venous thrombosis
Acute diseases
Systemic/localized infections
Aortic dissection
Burns
Hemorrhage
Pancreatitis
Trauma
Disseminated intravascular coagulation
Cyanotic heart disease with polycythemia
Others
Recent surgery
Thrombolytic therapy
Extracorporeal membrane oxygenation
Ventricular assist devices

any condition where fibrin production/breakdown is triggered. In an unselected hospital patient population, almost 80% have abnormal values of D-dimer [56]. Table 2.1 reports a list of the most common conditions leading to an increased D-dimer. However, D-dimer is highly sensitive to thromboembolic events, with a sensitivity of about 95% for acute mesenteric ischemia, cerebral venous thrombosis, acute aortic dissection, and pulmonary embolism. Therefore, its measure has a high negative predictive value, and on a clinical basis it should be used to exclude (when in normal range) rather than to diagnose (when increased) a specific thromboembolic event. Together with other diagnostic procedures (and namely imaging) D-dimer remains a cornerstone of the diagnostic process of suspected thromboembolism. Within this setting, the diagnosis of pulmonary embolism is paradigmatic,

and different algorithms like the Wells Score and the Revised Geneva Score combine clinical prediction rules with D-dimer measure.

2.5.2 D-Dimer in COVID-19

Since the early reports of COVID-19 series from China, elevated levels of D-dimer were a common finding. In the series of Wu and associates [9] patients with ARDS had a D-dimer double than patients without ARDS (1.16 μg/mL vs. 0.52 μg/mL) and non-survivors an eightfold higher value than survivors (3.95 μg/mL vs. 0.49 μg/mL). Wang and associates report D-dimer values to be significantly (P = 0.001) higher in ICU (414 mg/L) than in non-ICU patients (166 mg/L) [11] and similar differences were noticed by Huang and associates [12]. Chen and associates found abnormally elevated D-dimer levels in 36% of their patient population [10]. After these early reports, the finding of elevated values of D-dimer in COVID-19 patients, and of higher values in more severe cases, was confirmed by numerous reports from Western countries [21, 42–47, 51, 57, 58]. Significantly higher values of D-dimer were found in the most severe cases [42, 43, 45], in patients with thrombosis [45–47, 58], and in non-survivors [45]. The large body of literature on D-dimer in COVID-19 generated numerous meta-analyses pooling together different studies having, as dependent variable, the severity of the disease, and/or the survival. However, a critical appraisal of these pooled data is needed, given the heterogeneous modality of D-dimer value expression.

In a nice overview, Favaloro and Thachil pointed out the possible confounders in pooling together D-dimer values from different studies. Most publications did not identify the manufacturer and the assay used; most publications failed to report if DDU or FEU units were used; half the publications did not report the cutoff value; some publications did not report units of measure of D-dimer [59].

Given these limitations, the different meta-analyses offer a generally concordant scenario.

The existing meta-analyses express the D-dimer value as a continuous variable or as a binary (normal vs. elevated) variable. In the first case, given the different units of measure, the standardized mean difference (SMD) is used.

Shi and associates [60] analyzed 21 studies (3657 patients) and found that patients with a severe pattern of COVID-19 had a higher mean standardized value of D-dimer (SMD: 0.97, 95% confidence interval [CI] 0.77–1.17). The relative risk for severe pattern was 3.3 (95% CI 1.6–6.5) and for mortality 3.9 (95% CI 2.0–7.8) in patients with elevated D-dimer.

Sakka and associates [61] analyzed six studies (1355 patients) and found that non-survivors had an SMD of D-dimer values of 3.6 (95% CI 2.8–4.4). Simadibrata and associates [62] analyzed nine studies (2911 patients) and found a relative risk for mortality of 4.8 (95% CI 3.0–7.5) in patients with elevated D-dimer.

In a large series of 29 studies (4328 patients), Nugroho and associates [63] found that patients with severe patterns of the disease had an SMD of D-dimer values of 0.95 (95% CI 0.61–1.28) and those who did not survive had an SMD of 5.54 (95% CI 3.40–7.67). Shah and associates [64] analyzed 18 studies (3682 patients) and found that patients with severe patterns of the disease had an SMD of D-dimer values of 0.5 (95% CI 0.2–0.8) and those who did not survive had an SMD of 6.1 (95% CI 4.1–8.1). When D-dimers were expressed as binary variables, the relative risks for severe pattern and mortality were 2.0 (95% CI 1.3–3.1) and 4.1 (95% CI 2.5–6.8), respectively, in patients with elevated D-dimer.

Lima and associates [65] analyzed three studies only (648 patients) and found again that non-survivors had a significantly high SMD of D-dimers (3.37, 95% CI 1.53–5.02). Finally, Bansal and associates [66] used a composite outcome (mortality or severe patterns) analyzing six studies (1338 patients) and finding that the SMD of D-dimer values was 1.67 (95% CI 0.72–2.62) in those who fulfilled the composite outcome definition.

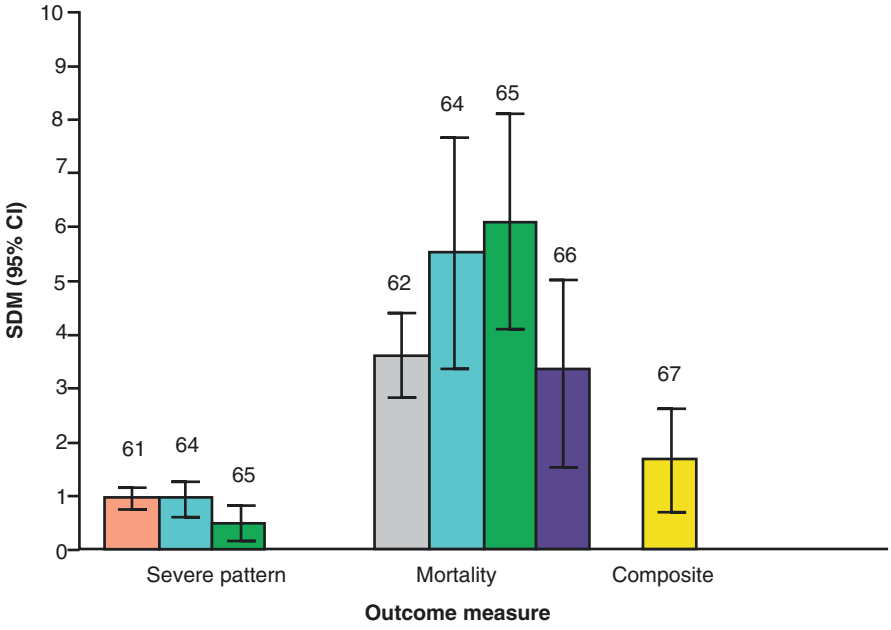

Fig. 2.2 Meta-analytic results of the association between D-dimer levels and severity of the disease, mortality, and composite outcome of severity + mortality. Numbers above the bars are the reference. *CI* confidence interval; *SDM* standardized mean difference

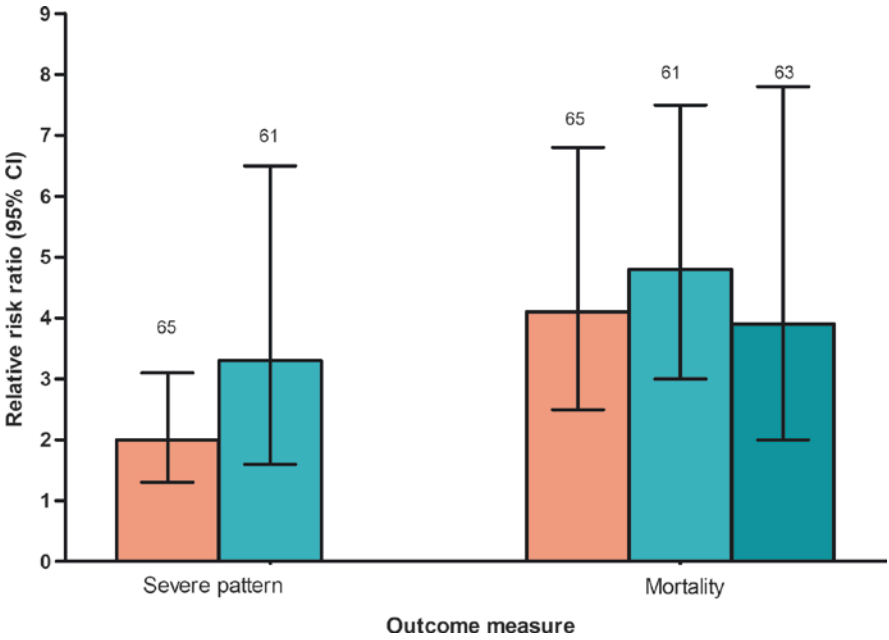

Fig. 2.3 Meta-analytic results of the association between elevated D-dimer and severity of the disease and mortality. Numbers above the bars are the reference. *CI* confidence interval

The data from the main existing meta-analyses are reported in Figs. 2.2 and 2.3. Overall the information is concordant in the finding that patients with severe patterns of the disease and moreover those who did not survive have higher values of D-dimer and that when considering D-dimer as a binary variable, patients with values above the cutoff have a double relative risk for severe patterns of the disease and a fourfold relative risk for mortality.

2.6 Conclusions

Even if routine coagulation tests have a low specificity for many infective coagulation-related disturbances, they are not useless in the setting of COVID-19, especially for the risk stratification of patients. Table 2.2 offers a summarized overview of the most common changes in routine coagulation tests in COVID-19 patients.

Table 2.2 Standard coagulation tests in COVID-19 acute respiratory syndrome patients

TEST	General population	Severe pattern	Thrombosis	Survival
PT	Normal in early phase	Slightly prolonged Prolonged in late phase with DIC	No specific modification	No differences between survivors and non-survivors
aPTT	Normal or shortened in early phase Prolonged in UFH treatment	Normal or shortened in ICU cases Prolonged in DIC	No specific modification	Shortened in non-survivors without DIC
Platelet count	Normal or increased in early phase	Decreased in ICU cases Decreased in DIC	Decreased in pulmonary embolism and other major thrombosis	Decreased in non-survivors
Fibrinogen	Increased	Increased in severe cases in some reports Decreasing trend in less severe cases Increased in high inflammatory state	Increased in some reports Decreased values in VTE and major thrombosis	Controversial reports of higher values in non-survivors
D-dimer	Increased	Increased in ICU patients Relative risk for severe pattern around 2.0 when > cutoff	Increased	Increased in non-survivors Relative risk for mortality around 4.0 when > cutoff

aPTT activated partial thromboplastin time, *DIC* disseminated intravascular coagulation, *ICU* intensive care unit, *PT* prothrombin time, *UFH* unfractionated heparin, *VTE* venous thromboembolism

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