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REVIEW



Alterations in platelets during SARS-CoV-2 infection

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Abstract

Coronavirus disease 2019 (COVID-19) is a pandemic syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. SARS-CoV-2 infection induces a process of inflammation and thrombosis supported by an altered platelet activation state. This platelet activation is peculiar being characterized by the formation of platelet-leukocytes rather than platelet-platelet aggregates and by an increased procoagulant potential supported by elevated levels of TF positive platelets and microvesicles.

Therapeutic strategies targeting, beyond systemic inflammation (i.e. with tocilizumab, an anti interleukin-6 receptor), this state of platelet activation might therefore be beneficial. Among the antithrombotic drugs proposed as candidates to treat patients with SARS-CoV-2 infection, antiplatelet drugs, such as aspirin are showing promising results.

Keywords

Antiplatelet drugs, coagulation, COVID-19, platelets, thrombosis

History

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Introduction

In December 2019, a new infectious disease outbreaked in China causing severe acute respiratory syndrome. The causative agent was identified as a new coronavirus, the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) [1]. The COVID-19 (Coronavirus Disease 2019) pandemic has led to high morbidity and mortality worldwide challenging healthcare systems and making crucial the identification not only of effective treatments but also of the pathogenic mechanisms.

Clinical features that characterize SARS-CoV-2 infection include inflammation and thrombosis [2,3]. Studies carried out so far have shown high levels of proinflammatory cytokines, the so-called "cytokine storm" that correlates with disease severity [4–6]. This exacerbated inflammatory state leads to the activation of coagulation, documented by levels of D-Dimer significantly elevated and predictive of mortality [7,8]. Additionally, levels of ferritin, factor VIII, von Willebrand Factor (VWF) and protein of the complement cascade are abnormal in COVID-19 [9–11]. These consistently reported hemostatic changes are indicative for a coagulopathy that may predispose COVID-19 patients to thrombotic events. Postmortem studies have indeed highlighted the presence of multiorgan thrombosis, even in patients on standard thromboprophylaxis [12,13]. Fibrin thrombi in the small arterial vessels were observed in 87% of the analyzed samples. Of note, pulmonary thrombosis was reported in 15% of COVID-19 patients. This incidence, which is similar to that reported in patients with SARS, is more than twofold higher than that

reported in patients with H1N1 influenza (6% of patients) [14]. These vascular microthrombi are particularly present in areas of diffuse alveolar damage and support the hypothesis that COVID-19 is complicated by coagulopathy and thrombosis [15].

In the context of this pandemic, platelets can be the potential pathophysiologic drivers of disease associated coagulopathy and thrombotic complications. The critical role of platelets during infections is well known [16]. It has been reported that several viruses, including influenza A virus, coronavirus, dengue virus human immunodeficiency virus type-1 (HIV-1) and adenovirus, are able to bind and activate platelets [17]. On the one side, however, the role of platelets may be beneficial, as they can reduce the circulating viral load by engulfing viruses and presenting them to neutrophils, as has been demonstrated for the influenza A virus [18]. On the other side, activated platelets can support the inflammatory process and tissue injury by worsening the pathological scenario. These cells may also foster the coagulation process by providing both tissue factor, the key protein for the initiation of the coagulation cascade, and the procoagulant surface for the assembly of coagulation factors and trigger the thrombotic process [19,20]. In addition, platelets can amplify inflammation through the release of soluble mediators from intracellular granules, the production of microvesicles and the interaction with leukocytes [21,22]. As a proof of these assumptions, an increased deposition of platelets and megakaryocytes [23,24] as well as an increased number of platelet-leukocyte aggregates has been reported within lung capillaries [15,25].

In this review, we will focus on the platelet alterations associated with COVID-19 disease summarizing changes occurring in platelet number, size, and function that recapitulate an overall state of platelet activation. We will also gain insight into the pharmacological strategies to manage platelet activation during COVID-19.45

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Alteration in Platelet Number and Size

Thrombocytopenia is a hallmark of various infectious diseases including MERS and SARS, pathologies in which it was recorded in 37% and 50% of affected patients, respectively [26,27]. It is therefore not surprising that a reduction, although mild, in platelet count is common feature also in patients with severe COVID-19 infection, with a 5–41% incidence depending on disease severity [28]. Several studies, included in a meta-analysis on 7613 COVID-19 patients, reported a significant relationship between thrombocytopenia and the clinical severity and mortality of COVID-19 [29]. Although platelet counts are often within reference ranges and severe thrombocytopenia rarely occurs, reduction of platelet count was identified as a poor prognostic factor [30]. A platelet count $<100 \times 10^9/L$ in the last 24 h before death in 60% of patients has been reported [31]. This dynamic change in platelet count seems to be peculiar of SARS-Cov-2 infection being not reported with other coronavirus strains [32].

Although changes in platelet number during the course of disease are multifactorial, in the context of infectious diseases a reduced platelet count may be due to decreased production of platelets in damaged lungs, as already described for SARS [33,34]. Alternatively, an increased platelet clearance may occur as a consequence of the activation of the immune system that induces an antibody-mediated phagocytic response [35]. Finally, the most likely hypothesis is that thrombocytopenia may be caused by increased consumption of platelets due to microthrombi formation [34]. This hypothesis is strengthened by the evidence that in COVID-19 patients there is a trend toward higher levels of immature reticulated platelets, indicative of active cell production by megakaryocytes in response to the increased platelet consumption [28]. This higher platelet turnover leads to the release of young macrothrombocytes that, as such, may account for the increased mean platelet volume found in COVID-19 patients [36–38].

Features of Platelet Activation in COVID-19

Platelet activation is a common feature of infection diseases and the degree of platelet activation follows the symptoms' severity. Several reports have shown that platelets from COVID-19 patients are hyperreactive, releasing into the blood both dense and alpha granules' cargo [38–44]. By measuring platelet adhesion to collagen under flow, Zaid et al. reported that both in severe and non-severe COVID-19 patients platelets are more prone to clotting [38]. Platelet aggregation is also higher than in healthy subjects especially when suboptimal concentrations of agonist are used. This lower platelet stimulation threshold in COVID-19 patients has been reported also by Manne et al., suggesting that infection primes platelet hyperreactivity. Interestingly, platelet aggregation is not increased when induced by stronger stimuli [46]. Furthermore, Pulcinelli et al. reported that it is even reduced in critically ill patients [38]. A similar behavior, together with an increased platelet agglutination – mediated by high levels of von Willebrand factor – has been previously described in patients with dengue virus infection [38]. This finding may be fitted with data reported in other studies showing that the expression of activated glycoprotein IIb/IIIa, the gold standard marker of platelet activation, is not altered [38,46].

Platelets respond to the increased systemic inflammation caused by COVID-19 associated cytokine storm increasing the interaction with leukocytes mainly through *P*-selectin. In accordance with data reported by other research groups [41,47], we have recently highlighted that in COVID-19 patients the higher levels of *P*-selectin, compared to healthy subjects, expressed on the platelet surface resulted in an enhanced (about 10-fold)

interaction with neutrophils and monocytes. Of note, this increased platelet–leukocyte interaction is a feature common also to other virus infection [48,47]. Interestingly, the number of platelet–leukocyte aggregates were significantly lower in critically ill patients compared to those with less severe infection and their levels were negatively associated with plasma levels of IL-6, CRP, and D-dimer, leading to the speculation of a possible involvement of platelet–leukocyte conjugates in microthrombotic events [38]. This hypothesis is supported by results from post-mortem studies demonstrating the presence of platelets, neutrophils, and thrombogenic neutrophil-extracellular traps (NETs), whose formation is sustained by platelet–neutrophil aggregates in the lung of COVID-19 patients [12,49,50].

Platelet–neutrophil interaction may also be responsible for the release of NETs, which are highly prothrombotic and, when dysregulated, able to induce intravascular coagulation. It has been shown indeed that sera from patients with COVID-19 contain highly specific markers for NETosis [51] and that NET formation is associated with thrombotic events in COVID-19 patients [40].

Platelet activation in COVID-19 patients also resulted in an increased release of extracellular vesicles (EVs) that might contribute to the COVID-19 pathogenesis [38,43,44]. In the last years, EVs received great attention as potential biomarkers for several human diseases including infections [52,53]. In the context of COVID-19, platelet EVs are strongly associated with SARS-CoV-2 infection, being higher in SARS-CoV-2 positive patients, regardless of the severity of the disease, compared to negative ones. This association is independent from any confounders making EVs a good diagnostic marker as indicated by ROC curve analysis [54].

Coagulation Abnormalities and Platelet Procoagulant Phenotype

Among the pathways and mediators that are dysregulated in COVID-19, coagulation disorders are prominent. The clotting abnormalities include prolonged prothrombin time (PT) and partial thromboplastin time (PTT), increased fibrinogen as well as D-dimer levels that are linked with a higher mortality rate [7,55]. An increased resistance to fibrinolysis has also been observed using viscoelastometric tests reinforcing the procoagulant state described in COVID-19 [56,57]. Patients with COVID-19 experience coagulopathies among which pulmonary thromboembolism [58,59], despite LMWH thromboprophylaxis [60] and a not well-defined intravascular coagulation syndrome, characterized by thrombotic events in the absence of a renal consumption coagulopathy and with an apparent lack of bleeding [61]. In a recently published meta-analysis including 20 studies in COVID-19 patients, Di Minno and collaborators have shown that the prevalence of venous thromboembolism (VTE) is ~30%. This percentage rises to 37% when considering only studies in which systematically the screening for thrombosis was carried out [62]. However, the complex relationship between SARS-CoV-2 infection and hemostatic imbalance observed in COVID-19 patients is not fully explained by the traditional risk factors for VTE and other factors seem to be responsible for the observed coagulopathy [62]. Among these, the procoagulant activity of platelets might have particular relevance. In addition to their role in primary hemostasis, platelets are indeed deeply involved in secondary hemostasis, providing not only the surface for the assembly of coagulation factors but also tissue factor (TF), the key protein required to initiate thrombin generation [19]. TF is a transmembrane protein that binds factor VII/VIIa leading to activation of the extrinsic coagulation pathway. TF-dependent activation of coagulation has been described in several viral

infections including Herpes simplex virus [63], human immunodeficiency virus (HIV) [64], dengue [65], or Ebola [66]. Different studies have reported increased TF expression in monocytes [41], endothelial cells [67] and extracellular vesicles [68] also in the context of SARS-CoV-2 infection, leading to the speculation that TF may be involved in the prothrombotic phenotype of this disease. We have provided evidence that in COVID-19 patients the number of TF expressing platelets is more than twice greater than that measured in healthy subjects, being higher in critically ill patients. Of note, the protein is functionally active and able to sustain thrombin generation [38]. Unlike the TF expressing platelets, the number of PS positive platelets in COVID-19 patients was comparable to that measured in healthy donors [15,69]. Consistent with the lack of PS exposure, dual-agonist stimulation of platelets from COVID-19 patients did not result in a significant loss of mitochondrial membrane potential [69]. Of interest, Althaus and collaborators highlighted that COVID-19 patients with diagnosis of thromboembolic complications had significantly higher PS externalization compared with those without thrombotic events. It remains unclear whether apoptosis alone is sufficient to support thromboembolic status in these patients or rather this is dependent on the generalized platelet activation state of SARS-CoV-2 disease [70].

The contribution of the extrinsic pathway to thrombosis in COVID-19 patients is further supported by data showing a significant increase in circulating extracellular vesicle-associated TF activity, which is linked with the severity of disease and mortality [71]. Of note, in COVID-19 patients, platelets together with erythrocytes are the main source of TF-positive MVs [38].

Potential Mechanisms Involved in Platelet Alterations in COVID-19

Several factors may contribute to the induction of the platelet hyperreactive state described in COVID-19 (Figure 1).

The activation of the immune system, which involves the production of cytokines and immune complements, whereas being essential for the resolution of the infection, can be the cause of immunothrombosis sustained by platelet activation. Circulating platelets can indeed be activated by soluble molecules (e.g. fibrinogen) and inflammatory cytokines, among which IL-6, IL-1b, and TNF-alpha, whose concentrations are significantly elevated in the plasma of COVID-19 patients [72]. Exposure of whole blood to IL-6 and IL-1β can lead to the amplification of platelet activation in response to common agonists, such as ADP or thrombin. In this regard, we have recently characterized the *in vitro* IL-6-mediated platelet stimulation, in terms of platelet-TF and P-selectin induction as well as of platelet-leukocyte formation. This cell activation, which is prevented by the presence of an IL-6 receptor antagonist, such as tocilizumab, closely mirrors the *in vivo* platelet activation observed in COVID-19 patients [38].

A second mechanism of platelet activation may lay in an alteration of their transcriptome. Infectious diseases including dengue, influenza, and sepsis are indeed associated with dynamic changes in platelet gene expression [73–75]. Similarly, in COVID-19 virus proliferation within lung tissue may induce activation of megakaryocyte leading to the production of platelets with a significantly altered gene expression profile. Of note, the COVID-19-associated transcriptome differs by hundreds of transcripts from that observed in influenza and sepsis suggesting a unique transcriptional footprint that characterizes SARS-CoV-2 infection [46].

Another hypothesis is that numerous COVID-19 comorbidities, typically associated with platelet function alterations, can cause a primed platelet state that worsens COVID-19 illness. Among these, metabolic syndrome, diabetes, gut dysbiosis,

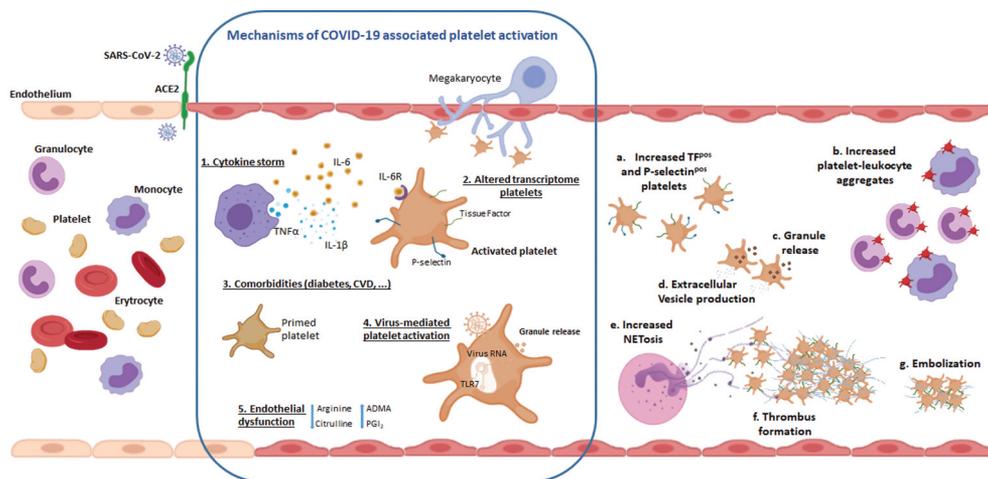


Figure 1. Platelet alterations in COVID-19 disease. As the SARS-Cov-2 infection progresses, the uncontrolled overproduction of inflammatory cytokines (1) may contribute to platelet activation resulting in increased exposure of P-selectin and Tissue Factor on the surface of circulating platelets. Platelet hyperreactivity may also be a consequence of the effect of SARS-CoV-2 on megakaryocytes. This results in the production of activated platelets characterized by significant changes in their transcriptome (2). Diabetes or cardiovascular diseases, characterized *di per se* by a sustained platelet activation state, may determine the presence in circulation of COVID-19 patients, of “primed platelets” more prone to activation (3). In addition, the altered platelet activation can be a direct consequence of the virus activity that, once internalized, can determine a Toll like receptor 7-mediated release of platelet granules (4). Finally, activation of endothelial cells, which is another hallmarks of COVID-19 disease, may result in a NO pathway dysfunction (5) that can promote and sustain further platelet activation. These mechanisms, which are not reciprocally exclusive, are responsible for (a) an increase in circulating procoagulant platelets expressing Tissue Factor, which are therefore able to support thrombin generation, and P-selectin-positive platelets available for the formation of heteroaggregates with monocytes and neutrophils (b). The release of alpha and dense granule cargo as well as the production of extracellular vesicles are further consequences of platelet activation (c,d). The interaction between platelets and neutrophils causes the formation of highly prothrombotic NETs (e) that can support the formation of fibrin-rich microthrombi that have been shown in the lung of COVID-19 patients (f,g).

cardiovascular disease, cancer, and aging are all conditions known to alter platelet functions [76–78].

Although SARS-CoV-2 RNA in blood is undetectable [38] or present at very low levels in less than 13% of patients with non-severe or severe COVID-19 [79,80], the possibility that the virus can directly activate platelets and/or megakaryocytes cannot be excluded. Indeed, this mechanism has already been described for dengue virus [81], influenza virus [48,82], human immunodeficiency virus-1 (HIV-1) [83], and encephalomyocarditis virus [73].

A putative receptor for the binding and entry of SARS-CoV-2 virus to cells is angiotensin converting enzyme-2 (ACE2) which is also expressed at high levels in the endothelial cells of the lung [84]. Many studies, however, did not detect ACE2 mRNA nor protein in platelets [43,46] not fully confirming the hypothesis that ACE2 is involved in this phenomenon. CD147 may be an alternative receptor for SARS-CoV-2 [85] as already described for SARS-CoV, HIV-1, and measles [86–88]. Although its involvement has been questioned [89], CD 147 is expressed in different cell types including leukocytes, endothelial cells, and platelets [90]. Within blood cells, its expression is higher in males than in females, in line with the prevalence of COVID-19 infection in male, and it is upregulated in asthma, chronic obstructive pulmonary disease, and obesity, that are reported risk factors underlying complications in COVID-19 [91]. Another receptor that might play a role in this presumed mechanism is furin. This convertase is implicated in the activation of the spike S-protein of SARS-CoV-2 [92] and is stored in large amount in platelets [93]. Langnau et al. have recently provided the evidence that plasma levels of furin are associated with poor clinical outcome in COVID-19 patients with cardiovascular diseases. The Authors did not provide the evidence that platelet-derived furin is implicated in SARS-CoV-2 activation, but they speculate that limiting its release by inhibiting platelet activation with antithrombotic drugs may be an effective strategy to prevent worst outcome [93].

Once internalized within platelets, the single strand viral RNA can interact with the Toll-like receptor 7 (TLR7) in the lysosome. Activation of TLR7 may then lead to the release of alpha granules with exposure of P-selectin and CD40L, which mediate interaction with leukocytes. In addition, TLR7 may also lead to the release of complement C3, which promotes the process of neutrophil NETosis [94,95].

Endothelial dysfunction, extensively described in COVID-19, might also be involved in the observed platelet changes. Endothelium synthesis of nitric oxide (NO) and prostaglandin I₂, two major molecules controlling platelet activation, is indeed deeply affected in COVID-19 patients. In these subjects, a marked reduction of arginine, which is involved in NO production and whose metabolism is modified by several viral infections [96], as well as a significant increase of ADMA, a specific NOS inhibitor, has also been reported [38]. The endothelial activation in COVID-19 patients is also documented by the significantly increased levels of prostacyclin that, as previously reported in other clinical settings, reflects the homeostatic response to inflammation and platelet activation [97].

Finally, as already described in influenza [98], it may also be hypothesized that, as the infection progresses and the adaptive immune response develops, platelets become further activated as a consequence of the interaction between platelet FcγRIIa and immunoglobulin G antibodies [99].

Possible Pharmacological Approaches

Despite today several different therapeutic strategies are used to treat SARS-CoV-2 infection, there is not yet a clear consensus on the pharmacological treatment of this disease (COVID-19

Treatment Guidelines Panel, NIH. Available at <https://www.covid19treatmentguidelines.nih.gov/>). To rapidly identify successful therapies to reduce COVID-19 mortality and morbidity, particular attention has been paid to the repurposing of existing drugs. The current therapeutic strategies are aimed at limiting the dysfunctional processes detected in COVID-19. Antiviral drugs are obviously used to inhibit replication of SARS-CoV-2. Immunomodulatory and anti-inflammatory treatments have proven effective in inhibiting the altered host immune response that leads to the exaggerated release of pro-inflammatory cytokines. Data summarized in two systematic reviews suggest that corticosteroid use in patients with severe COVID-19 disease is associated with reduced mortality [100,101]. Similarly, administration of tocilizumab, an anti-interleukin-6 receptor monoclonal antibody, reduced mortality, and promoted clinical improvement in patients with high concentration of circulating IL-6 [102]. Finally, evidence that the pathobiology of COVID-19 involves thrombosis has led to consideration of the possible efficacy of antiplatelet therapy.

Aspirin and P2Y₁₂ Antagonists

In addition to the well-established anti-inflammatory and antithrombotic properties [103], aspirin is effective in reducing replication, propagation, and infectivity of several DNA and RNA viruses, including different human coronavirus (such as the human CoV-229E and the MERS-CoV) [104,105].

Additionally, aspirin is able to reduce NETs' release in a sepsis model, thus limiting their potential to induce thrombin generation and drive intravascular coagulation [106]. Data in the literature reported that chronic intake of aspirin (100 mg/day) was effective in reducing mortality rate in patients with community-onset pneumonia compared to those not receiving the antiplatelet treatment (HR 2.07; 95% CI; 1.08–3.98; *p* = .029; for all-cause mortality) [107].

A recent meta-analysis of 10 cohort studies enrolling more than 680,000 patients with sepsis indicated that aspirin, administered before and after the onset of sepsis, reduced the rate of admission to ICU and of hospital mortality [108]. Aspirin is also effective in reducing the incidence of ARDS (OD 0.59, 95% CI, 0.36–0.98) [109]. Even clopidogrel administration, in association with an antiviral agent, improved survival rate during influenza infection in mice [47].

Altogether, these evidences provide the rationale for hypothesizing a benefit of pharmacological treatment of SARS-CoV-2 infection with these drugs. Thus, targeting both platelet activation as well as virus replication, antiplatelet drugs can be an effective therapeutic option.

To date, there are few observational studies reporting the effect of antiplatelet treatment with aspirin and/or antiP2Y₁₂ on COVID-19. In a very recent retrospective study, Chow et al. examined the association between aspirin use and the clinical outcome in 412 hospital-admitted COVID-19 patients. Even though the patients treated with the antiplatelet drug had higher rates of cardiovascular risk factors and coronary artery disease, aspirin treatment was independently associated with a reduced risk of mechanical ventilation, intensive care unit admission, as well as in-hospital mortality [110]. Accordingly, Liu and collaborators showed that low-dose aspirin treatment (100 mg/day) among hospitalized COVID-19 patients was associated with lower risk of mortality compared with a matched group of non-aspirin users [111]. Viecca et al. showed that the combined use of several antiplatelet therapies in severe COVID-19 patients with a thrombophilic profile improved gas exchange efficiency and increased arterial oxygenation [112]. Finally, we have provided the evidence that *in vitro* aspirin and the treatment with a P2Y₁₂ inhibitor prevent platelet activation induced by plasma of

COVID-19 patients [38]. The evidence that inhibition of P2Y₁₂ affects the release of sIL-6 R, the specific soluble receptor needed for IL-6 provides another possible mechanism underpinning the clinical efficacy observed in the treatment of COVID-19 [113].

Other pleiotropic effects can also be involved in the effectiveness of aspirin treatment, such as its effects on endothelial function. Aspirin increases NO availability by acetylating endothelial NO synthase (eNOS), by increasing the activity of dimethylarginine-dimethylaminohydrolase, which is responsible for the degradation of ADMA and by promoting the generation of 15-epi lipoxin A₄, which increases eNOS activity [114,115].

Finally, results obtained in a retrospective population-based cross-sectional study by Merzon and collaborators have recently suggested that preexisting treatment with low-dose aspirin might have a protective effect on COVID-19 susceptibility and disease duration among COVID-19-infected subjects [116]. This finding, if confirmed by appropriate trials, would even pave the way to the use of low-doses of aspirin for the prevention of COVID-19 infection.

The effectiveness of antithrombotic therapy certainly requires further investigation. Results of the RECOVERY trial have recently become available (currently unpublished and under peer-review) [117]. The study included more than 15000 patients randomized to receive aspirin or usual care alone. The data suggest that aspirin use is associated with an absolute reduction in thrombotic events (4.6% vs 5.3%) although it is not associated with a reduction in 28-day mortality. It should be mentioned, however, that, as the Authors stated, the rate of thromboembolic events in the studied population was lower compared to previous reports [118,119]. It is plausible therefore that aspirin might have more meaningful benefit in a higher thrombotic risk population. Several other randomized clinical trials are, however, currently in progress to clarify whether the use of antiplatelet drugs, such as aspirin (ClinicalTrials.gov Identifier: NCT04324463, NCT04365309, NCT04324463, NCT04363840) or clopidogrel (ClinicalTrials.gov Identifier: NCT02735707, NCT04409834; NCT04333407), could be potentially useful to mitigate the clinical consequence of SARS-CoV-2 infection.

Conclusion

In summary, during the acute phase of SARS-Cov-2 infection, platelets are characterized by an activated phenotype with enhanced TF expression, and release of extracellular vesicles together with a pronounced increase in the number of platelet-leukocyte aggregates. Activated platelets interact with neutrophils, promoting the process of NETosis, and with a dysfunctional endothelium inducing a prothrombotic phenotype. As the infection progresses, the cytokine storm first, and the interaction with antibody immunoglobulins later on can amplify platelet activation ultimately responsible for the prothrombotic scenario characterizing SARS-CoV-2 infection.

Data available on the effectiveness of aspirin and anti P2Y₁₂ provide a strong rationale for proposing the use of antiplatelet drugs in the treatment of COVID-19.

Declaration of interest

No potential competing interest was reported by the authors.

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