Subset of COVID-19 patients have increased bleeding risk

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The human body strives to keep itself in homeostasis, or balance. When blood clots are created, the body's innate response is to break the clots down to prevent significant health problems from arising.

Research has found that patients with COVID-19 are prone to serious blood clotting. This is why many patients receive high dose anticoagulants as part of their treatment.

But a new study in *Scientific Reports*, led by senior author Daniel Lawrence, Ph.D., a Professor of Basic Research in Cardiovascular Medicine at Michigan Medicine, found that aside from this heightened clotting risk, some COVID-19 patients have an unbalanced ability to break down clots as well, which is linked to a potential clinical biomarker seen in later stages of the disease.

This abnormal process of breaking down clots can contribute to a high bleeding risk, raising concerns about the current practice of giving COVID-19 patients high dose anticoagulants throughout the duration of their disease course.

This finding may be consistent with the NIH's recent decision to pause enrollment of critically ill COVID-19 patients in the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) trial, because "a potential for harm in this sub-group could not be excluded."

"Pathological blood clotting in COVID-19 patients has been studied extensively, but recognizing and addressing the high bleeding risk in a subgroup of patients is equally important," says first author Yu (Ray) Zuo, M.D., M.S.C.S., a rheumatologist at Michigan Medicine.

Zuo, Lawrence and their colleagues sought to understand the balance between COVID-19 coagulation and the breakdown of clots to help inform approaches to treatment.

The study included 118 COVID-19 patients and 30 healthy controls. In the COVID-19 patients, the team expected to see high levels of plasminogen activator-inhibitor-1, a molecule associated with stabilizing

blood clots. However, they didn't expect high levels of tissue-type plasminogen activator, the molecule responsible for removing the clots.

According to the researchers, almost half of the study's patients were supported by a ventilator and a quarter breathed just room air. Compared with the patients breathing room air, patients that required supplemental oxygen had significantly higher levels of plasminogen activator-inhibitor-1, but not of tissue-type plasminogen activator.

High levels of both tissue-type plasminogen activator (tPA) and plasminogen activator-inhibitor-1 (PAI-1) were associated with worse lung function, but high tPA independently correlated with mortality. The levels of either molecule can increase independently of the other, but the research also found a change in one can have consequences on the other.

The team asked whether COVID-19 plasma with the highest tPA levels might correlate with an enhanced, spontaneous breaking down of clots, as compared with low tPA COVID-19 plasma or control plasma.

After assessing 10 COVID-19 plasma samples with high tPA, 10 COVID-19 samples with low tPA and 10 healthy control plasma samples, it was clear the high-tPA COVID-19 samples were found to significantly enhance spontaneous clot breakdown compared to the other two groups.

This means that high tPA may be a biomarker for high bleeding risk and poorer outcomes in COVID-19, and supports further studies of tPA levels during the course of disease progression.

High levels of tPA tied to endothelial cells?
So, why do COVID-19 patients have such high levels of tPA in the first place?

Lawrence's team suspects the source of these high levels of tPA in COVID-19 patients, and the subsequent clotting issues, is because of damage to endothelial cells, which are cells that line blood vessels. If badly damaged, the blood vessels can actually break and cause bleeding.

The theory is that a hallmark symptom of COVID-19 ARDS, when fluid builds up in the lungs and causes trouble breathing and low oxygen levels in the blood, may trigger endothelial cell activation, which consequently promotes the release of tPA.

"In COVID-19 ARDS, activated neutrophils—one type of white blood cell—can aggregate in small vessels of lung and form inflammatory sticky spider web like structures that further activate and damage endothelial cells" says Zuo. "This process increases the release of tPA/PAI-1 in very sick COVID-19 patients."

Notably, the research team saw a strong correlation between tPA/PAI-1, neutrophil counts and circulating calprotectin, a known neutrophil activator.

"High dose anticoagulants have become standard COVID-19 treatment, but our study findings complicate the clinical picture," says Lawrence. "We urge caution regarding this recommendation, pending randomized studies, as COVID-19 clotting seems to be complex and potentially dynamic."

"We want to learn what groups of COVID-19 patients could benefit from high dose anticoagulants, and which patients could be hurt by it. Many providers are electing to be aggressive in treating the blood clotting, but we need to look at the body holistically, not just one piece of the puzzle. The body is complex and so is this disease," says Zuo. "As we learn more, we can develop a risk stratification tool so providers can make well-informed decisions."

More information: Yu Zuo et al, Plasma tissue plasminogen activator and plasminogen activator inhibitor-1 in hospitalized COVID-19 patients, *Scientific Reports* (2021). DOI: 10.1038/s41598-020-80010-z