

# Annexin A5 in Patients With Severe COVID-19 Disease: A Single-Center, Randomized, Double-Blind, Placebo-Controlled Feasibility Trial

**OBJECTIVES:** To evaluate the study design and feasibility of drug administration and safety in a randomized clinical trial of recombinant human annexin A5 (SY-005), a constitutively expressed protein with anti-inflammatory, antiapoptotic, and anticoagulant properties, in patients with severe coronavirus disease 2019 (COVID-19).

**DESIGN:** Double-blind, randomized clinical trial.

**SETTING:** Two ICUs at an academic medical center.

**PATIENTS/SUBJECTS:** Adults admitted to the ICU with a confirmed diagnosis of COVID-19 and requiring ventilatory or vasopressor support.

**INTERVENTIONS:** SY-005, a recombinant human annexin A5, at 50 or 100 µg/kg IV every 12 hours for 7 days.

**MEASUREMENTS AND MAIN RESULTS:** We enrolled 18 of the 55 eligible patients (33%) between April 21, 2021, and February 3, 2022. We administered 82% (196/238) of the anticipated doses of study medication and 86% (169/196) were given within 1 hour of the scheduled time. There were no drug-related serious adverse events. We captured 100% of the data that would be required for measuring clinical outcomes in a phase 2 or 3 trial.

**LIMITATIONS:** The small sample size was a result of decreasing admissions of patients with COVID-19, which triggered a stopping rule for the trial.

**CONCLUSIONS:** Although enrollment was low, administration of SY-005 to critically ill patients with COVID-19 every 12 hours for up to 7 days was feasible and safe. Further clinical trials of annexin A5 for the treatment of COVID-19 are warranted. Given reduction of severe COVID-19 disease, future studies should explore the safety and effectiveness of SY-005 use in non-COVID-related sepsis.

**KEYWORDS:** annexin A5; feasibility; safety; sepsis; severe coronavirus disease 2019; SY-005

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Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by the virus SARS-CoV-2. Although most people infected with this coronavirus show only mild symptoms, approximately 14% develop severe disease that requires hospitalization and oxygen support and 5% require admission to an ICU (1). Severe COVID-19 is complicated by acute respiratory distress syndrome, sepsis, thromboinflammation, and multiorgan failure (1, 2). Despite the availability of vaccines and therapies that target various stages of the disease (3), the disease is now endemic and causes ongoing morbidity and mortality, with 3.3 million cases and 23,000 fatalities globally more than 28 days in the weekly report for April 2023 from the World Health Organization (WHO) (4). Thus, the development of effective treatment for this

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## KEY POINTS

**Question:** Is a study of a novel drug, recombinant human annexin A5 (SY-005) with anti-inflammatory, antiapoptotic, and anticoagulant properties, feasible in patients with severe coronavirus disease 2019 (COVID-19)?

**Findings:** We successfully enrolled 18 patients, administered SY-005 to 82% of the anticipated doses of study drug, and did not observe any drug-related adverse events.

**Meaning:** SY-005 can be feasibly administered to patients with severe COVID-19 without serious adverse events. Further studies of SY-005 are warranted.

disease is essential for ongoing management of this global health crisis.

Annexin A5 is a constitutively expressed protein with anti-inflammatory, antiapoptotic, and anticoagulant properties (5). Preclinical studies in models of sepsis have shown potential therapeutic efficacy (6–8). Many of the potential mechanisms and benefits of annexin A5 including inhibition of the proinflammatory response and improved vascular endothelial function may apply in COVID-19 (6, 7, 9). A recombinant human annexin A5 (SY-005) has undergone phase 1 safety testing in healthy volunteers (ClinicalTrials.gov registration NCT04217629; results available at <https://osf.io/j5au9/>).

In this phase 2 randomized clinical trial, we evaluated the feasibility of administering SY-005 at doses of 50 or 100 µg/kg IV every 12 hours for 7 days to critically ill patients with severe COVID-19. The primary objective was assessed by enrollment metrics, protocol adherence, and safety parameters. The secondary objective was to evaluate clinical outcomes at day 30.

## METHODS

### Ethics

The study “Annexin A-5 in patients with severe COVID-19 disease” was approved by the Health Sciences Research Ethics Board (HSREB) at Western University on February 27, 2021, with project ID 116140. All procedures followed the ethical standards of the HSREB and the Helsinki

Declaration of 1975, as most recently amended (<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>). Consent was obtained for each participant from their substitute decision maker and affirmed from the participant when possible. The study was registered at ClinicalTrials.gov (NCT04748757).

An independent data safety monitoring board was established prior to receiving ethics approval as required by the HSREB.

### Trial Design

This was a three-arm randomized controlled feasibility trial (1:1:1; placebo:50 µg/kg SY-005:100 µg/kg SY-005) in two academic ICU. Blocked randomization with randomly permuted blocks of sizes 3 and 6 was used. Randomization was stratified by age at the time of enrollment (65 and < or >65 y) and by ICU. Randomization was performed by the study pharmacist or delegate using REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN) (10, 11) and all other study personnel and participants were blinded.

### Participants

Patients were eligible if they were 19 years old or older, had a positive polymerase chain reaction test for SARS-CoV-2 virus at any time during the current illness episode, and were receiving either vasopressors to maintain blood pressure after adequate fluid resuscitation based on clinical evaluation or respiratory support (including high-flow nasal oxygen but not conventional oxygen therapy). Exclusion criteria included known allergy to any of the ingredients or components of the investigational product (annexin A5, sorbitol, polysorbate 80), known pregnancy, moribund and not expected to survive beyond 24 hours, known or suspected risk for serious bleeding complications (such as platelets < 30, active and uncontrolled bleeding, ongoing full-dose therapeutic anticoagulation, or other risk for bleeding determined by the treating physician), or acute or chronic renal failure (dialysis-dependent) as evidenced by a serum creatinine more than two times the upper limit of normal, doubling of creatinine over the previous 24 hours (if available), or estimated creatinine clearance less than 50 mL/min/1.73 m<sup>2</sup> using the Chronic Kidney Disease Epidemiology Collaboration formula.

## Interventions

Participants were assigned to receive SY-005 50 or 100 µg/kg or saline placebo IV every 12 hours for 7 days. SY-005 was purchased from Suzhou Yabao Pharmaceutical R&D, China, after the approval of our clinical trial application was obtained from Health Canada (12). Information provided to Health Canada included the investigator's brochure, study protocol, informed consent form, quality overall statement for the production of SY-005, and a statistical analysis report for the phase 1 results (see <https://osf.io/j5au9/>). The selection of SY-005 doses was based on the binding affinity of annexin A5 to phosphatidylserine (7 nM) (13) and results of phase 1 trial in healthy subjects who were treated with SY-005 for up to 20 mg/d (equivalent of 333 µg/kg) for 7 days without any safety concerns. The intervention was stopped if therapeutic anticoagulation was started or if renal failure developed based on doubling of the serum creatinine from the baseline value, estimated glomerular filtration rate less than 50 mL/min/1.73 m<sup>2</sup> or initiation of renal replacement therapy. All other clinical decisions and management were left to the discretion of the attending healthcare team.

## Outcomes

For the primary outcome of study feasibility, we defined success as enrollment of at least 50% of eligible patients and 90% compliance or better with delivery of the intervention within 1 hour of scheduled doses. Enrollment was evaluated with the Consolidated Standards of Reporting Trials diagram. Metrics reported were the total enrollment rate and proportion of eligible patients. Protocol adherence was defined as the total number of doses given within 1 hour of the scheduled dose/total number of scheduled doses and total number of missed doses and reasons, as well as data completeness.

We also report on adverse events of special interest (bleeding complications), serious adverse events (SAEs), and evidence of new infections. SAEs of special interest were serious allergic reaction to the study drug, and hemorrhagic or bleeding complications defined as: 1) requiring transfusion of two or more units of packed red blood cells within 24 hours of an observed bleeding event, 2) a decrease in hemoglobin concentration of 20 g/L or more in less than 24 hours, or 3) any intracranial hemorrhage. Evidence

of new infections was any new positive culture result. Antidrug antibodies including antihuman annexin A5 IgG and IgM were assessed at day 1 pre-dose and at days 14 and 21 after study drug administration.

Secondary outcomes were the collection of data relevant for subsequent trials, such as hospital outcome, organ failure-free days, mortality, and organ dysfunction and respiratory failure as proposed by the COVID-19 Core Outcomes Set Investigators (14). If a patient was transferred back to their home healthcare region, patient outcome data were obtained by telephone.

## Sample Size

To inform the design of trials that will examine clinical outcomes, we aimed to enroll up to 60 patients over 18 months. Considering the uncertainty of the pandemic's evolution, the study was to be stopped before its completion if: 1) the intervention was associated with adverse events that called into question the safety of the intervention and 2) decreasing recruitment rate (<1 participant/mo for 3 mo). In addition, if the baseline Sequential Organ Failure Assessment (SOFA) score decreases from 3 (15, 16) to 2 with the 50 µg/kg dose and 1 with the 100 µg/kg SY-005 dose with SD of 2, a sample size of 63 patients has 80% power at 0.05 significance level (G-power v3.1.9.7 one-way analysis of variance available at <https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower>).

## Study Monitoring

Study monitoring included a review of the source records for the primary outcome measures.

## Statistical Methods

Continuous variables are described using median (IQR) and categorical variables are summarized as frequency (%). Participants who died prior to the 30-day follow up were assigned a SOFA score of 24, the worst possible value, to adjust for death. Because of the pilot nature of the study and the small sample size, we did not perform any hypotheses testing.

## RESULTS

De-identified, individual data are available at <https://doi.org/10.17605/OSF.IO/W2NSG>.

### Feasibility

As shown in **Figure 1**, 161 consecutively presenting patients who were admitted to the two participating ICUs with a diagnosis of COVID-19 were screened

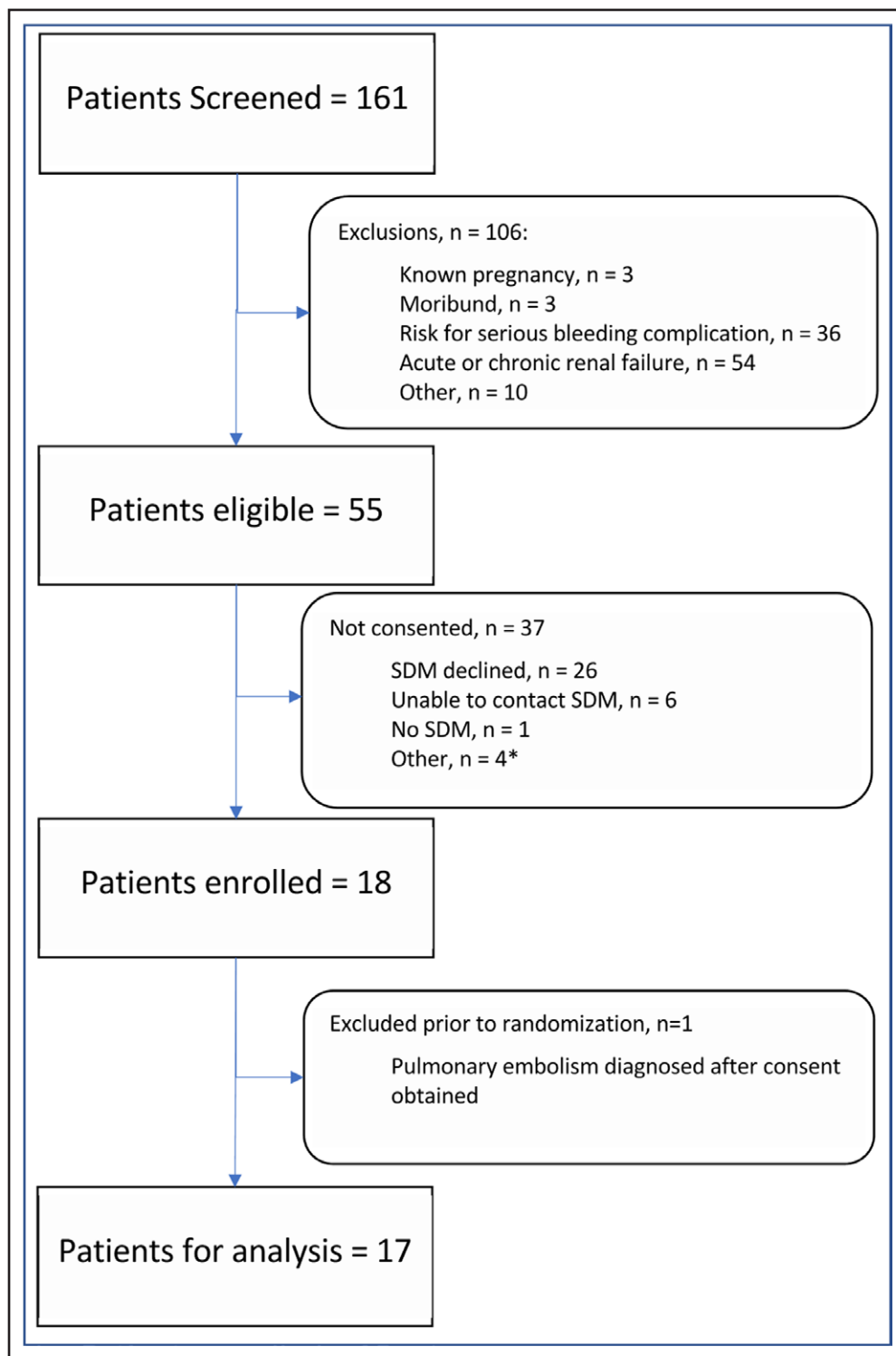
between April 21, 2021, and February 3, 2022, and we enrolled 18 of the 55 eligible patients (33%). As seen Figure 1, the common reasons for not enrolling patients were the risk for bleeding complications ( $n = 36$  [34%]), renal failure ( $n = 54$  [51%]), and substitute decision

makers declined consent for 25 of the 56 (45%) patients who met all eligibility criteria. The study was stopped based on the low enrollment rate as specified in the protocol.

Baseline characteristics demonstrate a young population without major comorbidities and with a high acute severity of illness as demonstrated by the WHO Clinical Progression Scale, nine equivalents of manpower score, multiple organ dysfunction score, and SOFA values (**Table S1**, <http://links.lww.com/CCX/B259>).

We administered 82% (196/238) of the anticipated doses of study medication. Reasons for discontinuing study drug were the finding of pulmonary embolism (one patient prior to the first dose or 14 doses, one patient had the final four doses discontinued), initiation of extracorporeal membrane oxygenation (two patients, 22 doses), death (one patient, one dose), and no reason documented (one patient, one dose). Among the administered doses, 86% (169/196) were given within 1 hour of the scheduled time.

Clinically important outcome data were obtained for all participants.



**Figure 1.** Consolidated Standards of Reporting Trials diagram showing flow of patients through the study. \*Two patients were improving and therefore not approached, and two patients were previously enrolled in the study. SDM = substitute decision maker.

Twelve protocol deviations in 10 patients were recorded. These included three deviations related to drug dosing (one dose was given after full-dose anticoagulation was started for a new diagnosis of pulmonary embolism, one patient received the 15th dose because of an error in the electronic order entry system configuration, and one patient did not receive their final dose for unknown reasons). Baseline bloodwork was obtained after the first dose of study drug in one patient, and one patient never received the study drug because of a diagnosis of pulmonary embolism that was made after randomization. The other protocol deviations were biomarker samples that were either missed or collected 1 day early or late due to staffing or clinical issues.

## Safety

One SAE was recorded in a patient who was discharged from hospital on day 14 and readmitted on day 29 with a diagnosis of deep venous thromboses and pulmonary emboli. This SAE was classified as unrelated to the study intervention.

New infections, blood transfusions, and biochemical data are summarized in the supplementary data (Tables S2–S6, <http://links.lww.com/CCX/B259>).

Overall, evidence of a new infection with at least one positive culture was found between days 1 and 30 in six of seven (86%) patients in the placebo group, three of four (75%) of patients in the low-dose group, and six of six (100%) of patients in the high-dose group. None of the patients receiving SY-005 received blood transfusions during the treatment period (days 1–8). We did not perform statistical testing of these data because of the small sample size. Inspection of the summary statistics and event rates (data not shown) did not suggest any significant safety issues. Antihuman annexin A5 IgG and IgM were assessed at day 1 pre-dose and at days 14 and 21 after study drug administration. All samples were negative for antiannexin A5 antibodies, indicating that no antidrug antibodies were detectable at 21 days after SY-005 administration.

## Clinical Outcomes

SOFA at day 30, the proposed primary outcome for a phase 3 randomized controlled trial, as well as other measures of severity of illness and the WHO Progression score, had a wide distribution in this small population with no apparent differences among the groups (Table 1).

**TABLE 1.**  
Clinical Outcomes

Parameter (Median, IQR)	Placebo (n = 7)	Annexin, 50 µg/kg (n = 4)	Annexin, 100 µg/kg (n = 6)	Annexin, Both Groups, (n = 10)
SOFA day 30	7 (0, 24)	1 (0, 13)	13 (0, 24)	1 (0, 24)
Delta SOFA (day 30–baseline)	0 (–7, 14)	–8 (–10, 4)	2 (–11, 13)	–9 (–11, 12)
Max SOFA	11 (10, 12)	12 (11, 14)	13 (11, 14)	13 (11, 14)
Delta max SOFA (max SOFA–baseline)	1 (0, 5)	3 (1, 5)	2 (0, 8)	2 (0, 4)
Max NEMS	45 (39, 45)	45 (45, 45)	39 (39, 45)	45 (39, 45)
Organ failure–free days (to 21 d)	0 (–1, 9)	5 (–1, 11)	–1 (–1, 0)	–1 (–1, 0)
ECMO, n (%)	2 (28.6)	0 (0.0)	1 (16.7)	1 (10.0)
WHO progression				
Max WHO	9 (9, 9)	9 (9, 9)	9 (9, 9)	9 (9, 9)
Delta WHO (max WHO–baseline)	1 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)
Mortality, hospital	3 (42.9%)	1 (25.0%)	3 (50.0%)	4 (40.0%)
ICU LOS (survivors), d	15.5 (10.7, 39.6)	12.3 (11.3, 23.5)	29.1 (24.0, 36.8)	23.7 (12.3, 29.1)
Hospital LOS (ICU survivors), d	26.5 (15, 58)	18 (16, 28)	48 (42, 59)	35 (18, 48)

ECMO = extracorporeal membrane oxygenation, LOS = length of stay, NEMS = nine equivalents of manpower score, SOFA = Sepsis Organ Failure Assessment, WHO = World Health Organization.

## DISCUSSION

In this pilot study, we demonstrated the feasibility of a randomized clinical trial design to evaluate annexin A5 as a novel therapeutic agent for treating critically ill patients with COVID-19. The major reason for not enrolling otherwise eligible patients was refusal of consent from the substitute decision makers. Common exclusion criteria were renal failure and the risk for hemorrhagic complications. Compliance with the protocol was high but failed to meet our prespecified criteria of 90%. We did not identify any obvious safety issues.

The global crisis created by the COVID-19 pandemic generated a prolific amount of research into management strategies and therapies. The most recent living guideline from the WHO recommends that patients with severe or critical COVID-19 receive treatment with corticosteroids, interleukin-6 receptor blockers and the Janus kinase inhibitor baricitinib (3). The interpretation of the rapidly evolving evidence is complex and requires consideration of the severity of COVID-19, patient characteristics and whether effects can be generalized to the drug class. The effect sizes from these interventions are modest; for example, 34 fewer deaths at 28 days per 1,000 patients treated with corticosteroids (3). Thus, there is a need for additional novel therapeutics to improve patient outcomes. Annexin A5 has potential mechanisms of action that target inflammatory and coagulant pathways that play important roles in the pathogenesis of COVID-19 (5, 17, 18). Although we chose to study patients who already had organ failure, it may be effective at earlier stages of the disease.

Strengths of our study include overcoming barriers to the investigation of a novel therapeutic during a pandemic. As independent investigators, we obtained SY-005, an investigational new drug, as it was being manufactured under license from our research institute as a potential therapeutic for sepsis. The manufacturer was completing phase 1 testing in healthy volunteers in 2019 and provided data to support our clinical trial application. We proceeded under the interim order issued by Health Canada, which expedited drug review and approval, and permitted remote written and nonwritten consent (12). All patients admitted to our ICUs with COVID-19 were screened for

eligibility. We used current recommendations to select our outcome measures (14) and successfully captured all required data elements. Additionally, no antiannexin A5 antibodies were detectable following 21 days of SY-005 administration, suggesting that SY-005 does not induce an antidrug immune response in patients with severe COVID-19.

Limitations of our study include a sample size smaller than planned. Two exclusion criteria, renal failure because the drug is cleared through the kidney and bleeding risk based on the drug's mechanism of action, were based on theoretical safety concerns. These caused the exclusion of otherwise eligible patients. Our pending analysis of pharmacokinetic and pharmacodynamic effects from this study may provide evidence for modifying those exclusion criteria. We also experienced many consent refusals, which may appropriately reflect patient beliefs but also the inability to have face-to-face encounters during the consent process. Future studies could employ mixed methods to explore why substitute decision makers decline consent to critical care trials, and whether interventions such as shorter letters of information and the use of videos and graphics can improve enrollment.

In conclusion, SY-005 can be feasibly administered to critically ill patients with COVID-19 every 12 hours for up to 7 days without apparent SAEs. Further clinical trials of annexin A5 for the treatment of COVID-19 are warranted. Pharmacokinetic analysis and investigation into the interaction with traditional anticoagulants may support more liberal inclusion criteria. The use in nonsevere COVID-19, and non-COVID-19 sepsis, may also be appropriate and deserves further investigation.

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Drs. Lu and Feng are two of the three co-inventors of a patent owned by Lawson Health Research Institute on annexin and its use to treat inflammatory disorders. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Drs. Martin and Feng conceived and designed the study. Drs. Campbell, Bentall, Tschirhart, Lu, and Priestap contributed to data collection or analysis. Dr. Fraser collected, processed, and stored blood samples. Drs. Slessarev, Leligdowicz, Mele, Basmaji, and Ball contributed to study design, enrolment, and oversight. The manuscript was drafted by Dr. Martin. All authors reviewed, revised, and provided final approval to the manuscript.

For information regarding this article, E-mail: [cmartin1@uwo.ca](mailto:cmartin1@uwo.ca) [ClinicalTrials.gov](https://ClinicalTrials.gov): NCT04748757.

De-identified individual data is available at <https://osf.io/w2nsg>.

## REFERENCES

1. Zhou F, Yu T, Du R, et al: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* 2020; 395:1054–1062
2. Bonaventura A, Vecchié A, Dagna L, et al: Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. *Nat Rev Immunol* 2021; 21:319–329
3. Clinical management of COVID-19: Living guideline. Geneva, Switzerland, World Health Organization, 2023
4. World Health Organization. Weekly epidemiological update on COVID-19. Available at: <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---6-april-2023>. Accessed April 6, 2023
5. Mui L, Martin CM, Tschirhart BJ, et al: Therapeutic potential of annexins in sepsis and COVID-19. *Front Pharmacol* 2021; 12:2377
6. Arnold P, Lu X, Amirahmadi F, et al: Recombinant human annexin A5 inhibits proinflammatory response and improves cardiac function and survival in mice with endotoxemia. *Crit Care Med* 2014; 42:e32–e41
7. Park JH, Jang JH, Choi EJ, et al: Annexin A5 increases survival in murine sepsis model by inhibiting HMGB1-mediated pro-inflammation and coagulation. *Mol Med Camb Mass* 2016; 22:424–436
8. Hu G: Recombinant human annexin A5: A novel drug candidate for treatment of sepsis? *Crit Care Med* 2014; 42:219–220
9. Ewing MM, de Vries MR, Nordzell M, et al: Annexin A5 therapy attenuates vascular inflammation and remodeling and improves endothelial function in mice. *Arter Thromb Vasc Biol* 2011; 31:95–101
10. Harris PA, Taylor R, Thielke R, et al: Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42:377–381
11. Harris PA, Taylor R, Minor BL, et al; REDCap Consortium: The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; 95:103208
12. Canada.ca: ARCHIVED Interim Order No. 2 Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19. Available at: <https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/interim-order-2-clinical-trials-medical-devices-drugs.html>. Accessed March 17, 2023
13. Blankenberg F, Narula J, Strauss HW: In vivo detection of apoptotic cell death: A necessary measurement for evaluating therapy for myocarditis, ischemia, and heart failure. *J Nucl Cardiol* 1999; 6:531–539
14. Tong A, Elliott JH, Azevedo LC, et al: Core outcomes set for trials in people with coronavirus disease 2019. *Crit Care Med* 2020; 49:503–516
15. Liu M, Maxwell CJ, Armstrong P, et al: COVID-19 in long-term care homes in Ontario and British Columbia. *CMAJ* 2020; 192:E1540–E1546. doi:10.1503/cmaj.201860
16. Fraser DD, Slessarev M, Martin CM, et al: Metabolomics profiling of critically ill coronavirus disease 2019 patients: identification of diagnostic and prognostic biomarkers. *Crit Care Explor* 2020; 2:e0272
17. Kennedy JR: Phosphatidylserine's role in Ebola's inflammatory cytokine storm and hemorrhagic consumptive coagulopathy and the therapeutic potential of annexin V. *Med Hypotheses* 2020; 135:109462
18. Argañaraz GA, Palmeira J da F, Argañaraz ER: Phosphatidylserine inside out: a possible underlying mechanism in the inflammation and coagulation abnormalities of COVID-19. *Cell Commun Signal* 2020; 18:190