Stem Cells and Development
Stem Cells Dev. June 15, 2020; 29(12): 747–754.
Published online 2020 Jun 11. doi: 10.1089/scd.2020.0080
PMCID: PMC7310206
PMID: 32380908

Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19

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BUT READERS DEMANDED DESCRIPTION & IDENTIFICATION OF EXOFLO: see Lim et. al.

LIM ET. AL DEMAND CLARIFICATION.pdf

Abstract

This prospective nonrandomized open-label cohort study addresses the safety and efficacy of exosomes (ExoFlo™) derived from allogeneic bone marrow mesenchymal stem cells as treatment for severe COVID-19. During April 2020, ExoFlo was provided to 24 SARS-CoV-2 polymerase chain reaction-positive patients at a single hospital center, all of whom met criteria for severe COVID-19 as well as moderate-to-severe acute respiratory distress syndrome. Patients received a single 15 mL intravenous dose of ExoFlo and were evaluated for both safety and efficacy from days 1 to 14 post-treatment. All safety endpoints were met with no adverse events observed within 72 h of ExoFlo administration. A survival rate of 83% was observed. In total, 17 of 24 (71%) patients recovered, 3 of 24 (13%) patients remained critically ill though stable, and 4 of 24 (16%) patients expired for reasons unrelated to the treatment. Overall, after one treatment, patients' clinical status and oxygenation improved with an average pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) increase of 192% ($P < 0.001$). Laboratory values revealed significant improvements in absolute neutrophil count [mean reduction 32% (P value <0.001)] and lymphopenia with average $CD3^+$, $CD4^+$, and $CD8^+$ lymphocyte counts increasing by 46% ($P < 0.05$), 45% ($P < 0.05$), and 46% ($P < 0.001$), respectively. Likewise, acute phase reactants declined, with mean C-reactive protein, ferritin, and D-dimer reduction of 77% ($P < 0.001$), 43% ($P < 0.001$), and 42% ($P < 0.05$), respectively. In conclusion, owing to its safety profile, capacity to restore oxygenation, downregulate cytokine storm, and reconstitute immunity, ExoFlo is a promising therapeutic candidate for severe COVID-19. Future randomized controlled trials (RCTs) are needed to determine ExoFlo therapeutic potential.

Keywords: exosome, MSC, COVID-19, ARDS, bone marrow, SARS-CoV-2

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Introduction

COVID-19, the disease caused by the SARS-CoV-2 coronavirus, has rapidly expanded into a global pandemic. Owing to the explosion of cases, concerns regarding resource limitations and emerging understanding of how best to treat COVID-19, hospitals have developed increasing thresholds for hospital admission as well as mechanical ventilation [1]. Before the pandemic, patients presenting with fever, dyspnea, and hypoxia, and meeting criteria for moderate-to-severe acute respiratory distress syndrome (ARDS), would typically be intubated. However, these patients are now first maintained with noninvasive supplemental O_2 and other optimization measures such as proning, with endotracheal intubation being delayed as long as possible. This group of patients holds particular interest for this study, as early intervention could substantially

reduce progression to hypoxic respiratory failure requiring mechanical ventilation, a clinical event associated with mortality rates estimated as high as 67%–94% [2–4].

Trials for experimental single target agents, including antivirals, antibiotics, and biologics, such as remdesivir, hydroxychloroquine, and tocilizumab, respectively, have yielded mixed outcomes with some associated with significant morbidity and mortality [5–8]. Other options for prevention and treatment include vaccination and convalescent plasma, both of which require stable viral epitopes for their efficacy. But much like HIV, the SARS-CoV-2 RNA virus mutates rapidly and directly suppresses host T cell function, which may ultimately render these therapies ineffective [9]. Clinically, this has been borne out with frequent presentations of multiorgan failure in the setting of immunodeficiency even in previously healthy individuals.

Central to COVID-19 disease progression is the development of cytokine storm, which is thought to be sustained and amplified by evolving parallel processes: (1) the activation of macrophages and other antigen presenting cells, alerting lymphocytes to the presence of the virus, (2) viral RNA replication within host cells, activating synthesis of proinflammatory factors, and (3) viral invasion of lymphocytes, eliciting lymphocyte apoptosis and facilitating ongoing immune evasion [10,11]. The complex pathophysiology suggests that severe COVID-19 is more amenable to treatment with a pleiotropic agent rather than a single target agent.

Although allogeneic bone marrow mesenchymal stem cell (bmMSC) transplantation has shown promise, with trials currently underway, this technology is limited by safety, cell survivability, scalability, and regulatory issues that make it an impractical option to meet the needs of millions of infected patients worldwide [12–14]. However, bone marrow derived exosomes, a complex mix of signaling nanovesicles secreted by bmMSCs, are a novel, multitargeted, next generation biologic agent that could be the key to downregulating the cytokine storm, and to reversing the suppression of host antiviral defenses that characterize COVID-19 [15]. Containing a panoply of chemokines, growth factors, mRNA, and microRNA with anti-inflammatory, regenerative, and immunomodulatory functions, exosomes are the paracrine and endocrine mediators that confer bmMSCs with their healing properties, a fact that taken together with their superior safety profile, stability, and scalability, makes exosomes a tantalizing, practical, and yet unexplored treatment option for COVID-19 [15–18]. Multiple preclinical studies have shown favorable therapeutic effects of bone marrow-derived exosomes delivered intravenously in animal models of acute lung injury, ARDS, asthma, and other inflammatory diseases, with analyses revealing reduced alveolar inflammation, enhanced edema clearance, restoration of leaky epithelial membranes, and other sequelae of cytokine storm [19–24].

ExoFlo™, a bmMSC-derived exosome agent, is tested for sterility and processed and stored in FDA-registered facilities that meet Current Good Manufacturing Practices (CGMP) and Current Good Tissue Practices (CGTP), thereby meeting key standards for safety profile, tissue traceability and comprehensive instructions for use (IFU), was administered intravenously to 24 patients with SARS-CoV-2 associated ARDS who were clinically deteriorating. The objectives were to evaluate, after a single dose of intravenous ExoFlo, for safety including infusion reactions and any adverse events as well as efficacy including overall status as evidenced by disposition, oxygenation as evidenced by partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) and oxygen support requirements, degree of inflammation,

and immunocompetence, as evidenced by levels of C-reactive protein (CRP), D-dimer, ferritin, and cell counts of neutrophils and T lymphocytes.

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Methods

Patients were enrolled in a prospective nonblinded nonrandomized primary safety trial at a single hospital center from April 8 to 28, 2020. All COVID-19 patients admitted to hospital, meeting acceptance criteria, were offered the therapeutic intervention. Inclusion criteria included age 18–85 years, positive result on SARS-CoV-2 polymerase chain reaction (PCR) (treatment may be initiated before PCR confirmation if known exposure to COVID-19-positive contact, but ultimately, result has to be positive), and presentation of fever and/or dyspnea for >72 h, overall clinical deterioration as evidenced by downtrending PaO_2/FiO_2 ratio. All patients were already initiated on hydroxychloroquine and azithromycin in the emergency department (ED) or as an outpatient, which was the institutional and local practice in early to mid-April 2020. Exclusion criteria included pregnancy, severe pre-existing cardiopulmonary, renal, hepatic, and hematologic disease, immunodeficiency secondary to other viruses, severe metabolic disturbances (pH <7.3), and evidence of irreversible coagulopathy (eg, frequently occluded vascular access) or disseminated intravascular coagulation (eg, profuse bleeding from endotracheal tube, lines, and foley).

Written informed consent for receiving treatment derived from allogeneic stem cells was obtained after the initial discussion with the patient or health care proxy. Initial screening included a review of medical history, physical examination, vitals during hospitalization, pertinent laboratories and studies, and applicable objective parameters pertaining to critical care support, for example, ventilator settings, vasopressors, inotropes, and temporary dialysis requirements. In total, 51 patients were considered for eligibility; 27 patients who met acceptance criteria were enrolled into the following three study cohorts (Fig. 1):

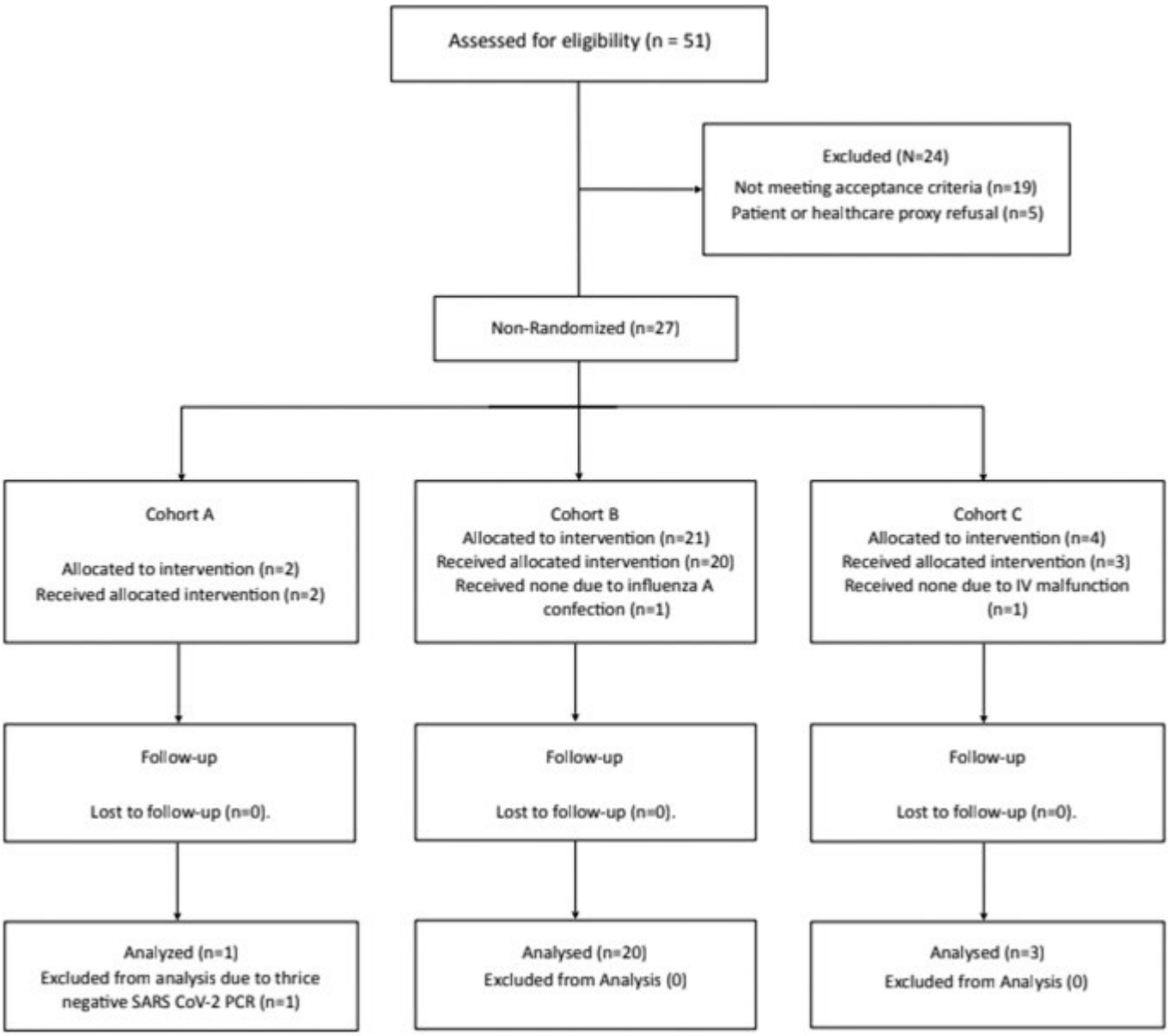

FIG. 1.

Consort diagram for study enrollment, allocation of intervention, follow-up, and analysis.

Cohort A ($n = 2$)

This cohort included COVID-19 outpatients with fever and dyspnea with objective vitals of respiratory rate (RR) ≥20 and/or SpO_2 <94% on room air (RA). One patient, who was presumed COVID-19 positive, was excluded after the pending COVID-19 test returned negative.

Cohort B ($n = 21$)

This cohort included COVID-19 in-patients with hypoxemia as defined by SpO_2 ≤90% on RA or patients who require supplemental oxygen to maintain SpO_2 ≥94%, who require noninvasive

oxygen support, which includes the following modalities: nasal cannula, nonrebreather, noninvasive positive pressure ventilation such as bilevel positive airway pressure, and high flow nasal cannula oxygen. One patient was excluded due to influenza A coinfection.

Cohort C ($n = 4$)

This cohort included intubated COVID-19 patients with hypoxic respiratory failure on mechanical ventilation. One patient was excluded due to an IV malfunction during administration of ExoFlo.

Administration dose and route

In total, 15 ml of ExoFlo was added to 100 mL of normal saline and administered intravenously for 60 min.

Assessments

Before infusion, on the day of treatment, baseline testing was performed for the following parameters: SARS-CoV-2 PCR, BMP, CBC, PT/INR, LFT, ESR, CRP, ferritin, D-dimer, T lymphocyte panel, mycoplasma IgM, Legionella Ag,Strep Pneumoniae Ag, influenza A/B, urinalysis/urine culture, blood culture, HgbA1c, blood type and screen, chest X-ray, and EKG. Vital signs were monitored $T = 5$, $T = 10$, $T = 15$, $T = 30$, $T = 45$, and $T = 60$ min after infusion initiation, then hourly for the first 6 h postinfusion, every 3–4 h thereafter per hospital standards. For inpatients, laboratory collection and direct clinical evaluation were performed on the day of treatment before the infusion and repeated for days 1–14 post-treatment or until the final day of hospitalization, with flow cytometry data collected for the first 5 days after receiving ExoFlo. For outpatients, laboratory collection and direct clinical evaluation were performed on the day of treatment before the infusion and repeated daily until recovery.

Study oversight

The study protocol was reviewed and approved by Christ Hospital's institutional review board (approval number IRB 2020.01) under emergency compassionate use rules for immediate enrollment. Written informed consent was obtained for all patients in accordance with local regulations. The program was designed and conducted by the primary and coinvestigators who collected the data, monitored the conduct of the program, and performed the statistical analysis. All authors had access to the data and assumed responsibility for the integrity and completeness of the reported data. The IRB protocol was prepared by the primary investigator. All adverse outcomes were reviewed by an independent data safety monitoring board (DSMB).

Statistical analysis

Assessment of pre- and post-treatment data sets was performed using paired *t*-test analysis on GraphPad Prism 8.0. No additional correlative analysis or multivariate analyses were performed. No sample size calculations were performed. All COVID-19 patients admitted to hospital, meeting acceptance criteria, were offered the therapeutic intervention. The analysis population

included all patients who received their first dose of ExoFlo before April 14, 2020, and for whom clinical data for at least one subsequent day were available.

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Results

Baseline patient characteristics

Baseline demographic and clinical patients' characteristics are reported in Table 1. Seventeen males (age range: 45–84 years) and 10 females (age range: 29–75 years) were enrolled from April 6 to April 13, 2020. Of the 27 patients enrolled and treated, 3 were excluded for the following: 1—thrice negative for COVID-19 PCR test, and 1—influenza-A coinfection, and 1—IV malfunction. Percentages of patients by race were 30% Caucasian, 63% Hispanic, and 7% Asian. Patients with pre-existing conditions comprised 93% of the population. Prediabetic and type 2 diabetic patients comprised 86% of the population whereas hypertension comprised 44.4%.

Table 1.

Clinical Demographics

Baseline demographics and pretreatment conditions of enrolled participants

		Total (*n* = 27)	**Cohort A (*n* = 2)**	**Cohort B (*n* = 21)**	**Cohort C (*n* = 4)**
Age (years)	Range (median)	29–84 (59)	49–84	45–75 (62)	29–66 (54)
	<50	8	1	6	1
	50 to <70	14	—	11	3
	≥70	5	1	4	0
Gender	Male	17	2	14	1
	Female	10	0	7	3
Body mass index	Weight (kg)/height (m)^2	29.7	28.5	29	34.3
O_2 support category	Mechanical ventilation	2	0	0	2
	BI-PAP	2	0	2	0
	High flow oxygen (HFNC)	5	—	4	1
	NRB	10	0	11	0
	NC	4	1	3	—
	Room air	1	1	—	—

Baseline demographics and pretreatment conditions of enrolled participants

		Total ($n = 27$)	Cohort A ($n = 2$)	Cohort B ($n = 21$)	Cohort C ($n = 4$)
Illness before treatment	Duration (days)	15	6.5	16	11.3
Illness before admission	Duration (days)	8.5	N/A	9.6	1.7
Pre-existing comorbidities	Pre-T2DM	3	0	1	2
	T2DM	20	1	18	1
	Hypertension	12	1	10	1
	Hyperlipidemia	5	1	4	0
	Any condition	25	2	20	3
Stage of ARDS (PaO_2/FiO_2)	Mild (200 to ≤300)	1	1	0	0
	Moderate (100 to ≤200)	11	1	10	0
	Severe (<100)	13	0	9	4

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All participants met criteria for moderate-to-severe ARDS based on clinical presentation, acute onset, noncardiogenic etiology, and PaO_2/FiO_2 ratio ≤200 mmHg. In total, 86% of the patients in the study had either T2DM or pre-T2DM. Although the early stages of the COVID-19–associated viral pneumonia may not be entirely consistent with ARDS in many patients, PaO_2/FiO_2 ratio remains a vital oxygenation metric.

ARDS, acute respiratory distress syndrome; BI-PAP, bilevel positive airway pressure; FiO_2, fraction of inspired oxygen ratio; HFNC, high flow nasal cannula; PaO_2, pressure of arterial oxygen; NC, nasal cannula; NRB, nonrebreather; T2DM, type 2 diabetes mellitus.

Safety

No infusion reaction or adverse events were observed in any cohort within the first 72 h. No adverse events were attributable to administration of ExoFlo. Adverse events in Table 2 included worsening hypoxic respiratory failure requiring intubation ($n = 4$), pulmonary embolism ($n = 1$), acute renal failure ($n = 3$), and expiration ($n = 4$)—all events occurring >72 h after treatment in seven patients, which were evaluated by the DSMB to be reasonably attributable to COVID-19 progression or to a clear temporally correlated provoking stimulus.

Table 2.

Adverse Event Log

All adverse events including outcomes not likely associated with treatment

PostTx day	Cohort A ($n = 2$)	Cohort B ($n = 21$)	Cohort C ($n = 4$)	Total events
0–1	0	0	0	Pulmonary embolus $n = 1$
2	0	0	0	Respiratory failure $n = 4$
3	0	0	0	Acute renal failure $n = 3$
4	0	Expiration ($n = 1$)	0	Expiration $n = 4$
5	0	Respiratory failure ($n = 1$)	Expiration ($n = 1$)	
6	0	Respiratory failure ($n = 2$)	0	
7	0	0	0	
8	0	0	0	
9	0	Acute renal failure ($n = 1$)	0	
10	0	Respiratory failure ($n = 1$)	0	
11	0	Acute renal failure ($n = 1$)	0	
12	0	Expiration ($n = 1$), pulmonary embolus ($n = 1$)	0	
13	0	Acute renal failure ($n = 1$)	Expiration ($n = 1$)	
14	0	0	0	

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All adverse events were reviewed by an independent DSMB. None of the adverse events were attributable to the therapeutic intervention.

DSMB, data safety monitoring board.

Overall clinical outcome

The survival rate in the study was 83%. In total 71% of the patients (17/24) recovered and/or were discharged from the hospital after a mean of 5.6 days after intravenous ExoFlo administration. A total of 16% of the patients (4/24) expired and 13% of the patients (3/24) remained critically ill, requiring mechanical ventilation and intensive care.

Oxygenation

Oxygenation was assessed by calculating partial PaO_2 to FiO_2 as well as tracking oxygen support requirement at baseline, on day of treatment, and days 1–14 after administration of the ExoFlo. In total, 80% of patients (20/24) exhibited improved PaO_2/FiO_2 ratio within 3 days of treatment.

The mean increase of PaO_2/FiO_2 from baseline to day 14 post-ExoFlo treatment or final day of hospitalization was 191% ($P < 0.001$) and correlated with the reduced requirement of oxygen support as shown in Fig. 2. Optimal responders exhibited PaO_2/FiO_2 of 200 mmHg by day 3 after ExoFlo treatment, which was a strong predictor of hospital discharge; suboptimal responders were noted to exhibit slight improvement of PaO_2/FiO_2 but not >200 mmHg by day 3.

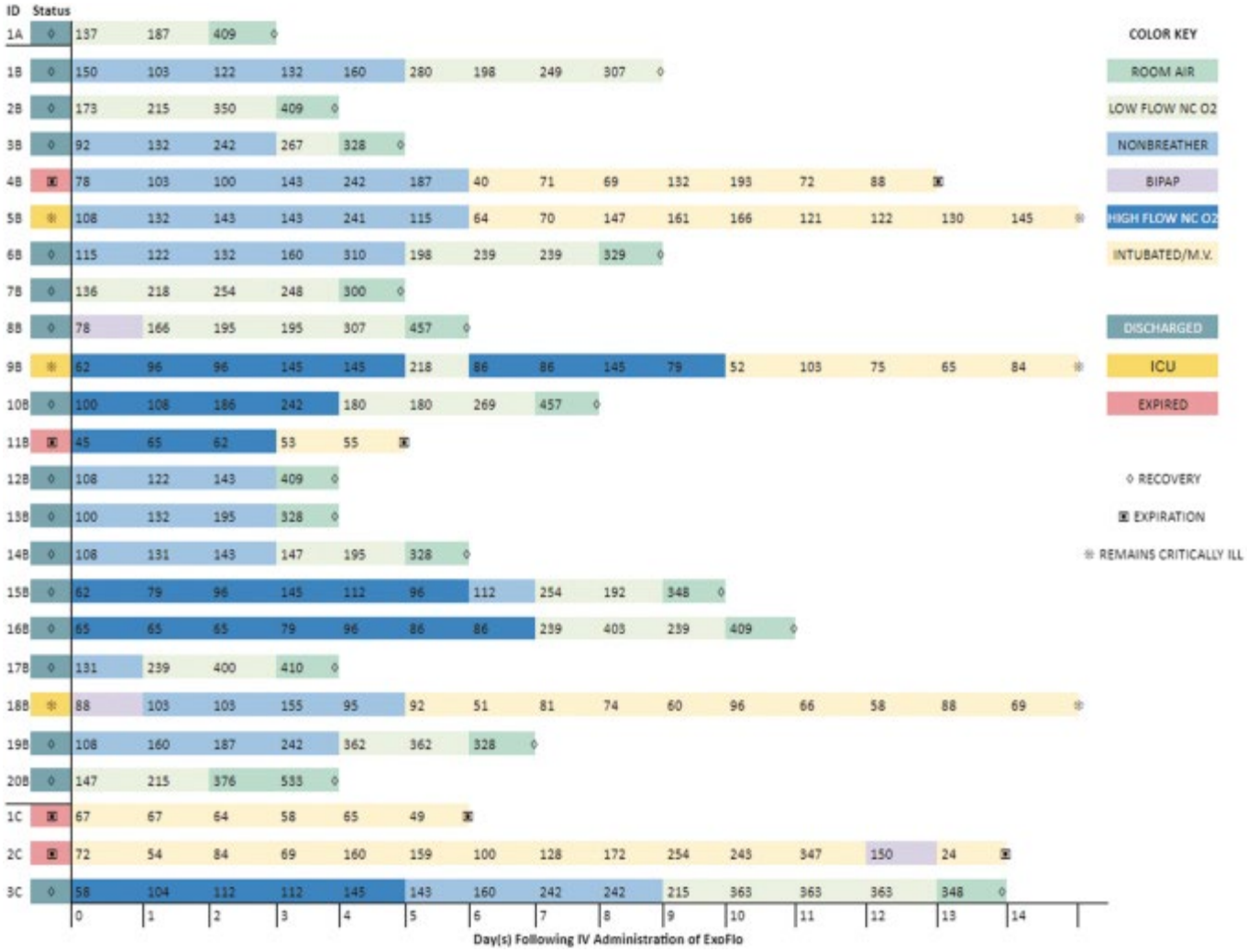


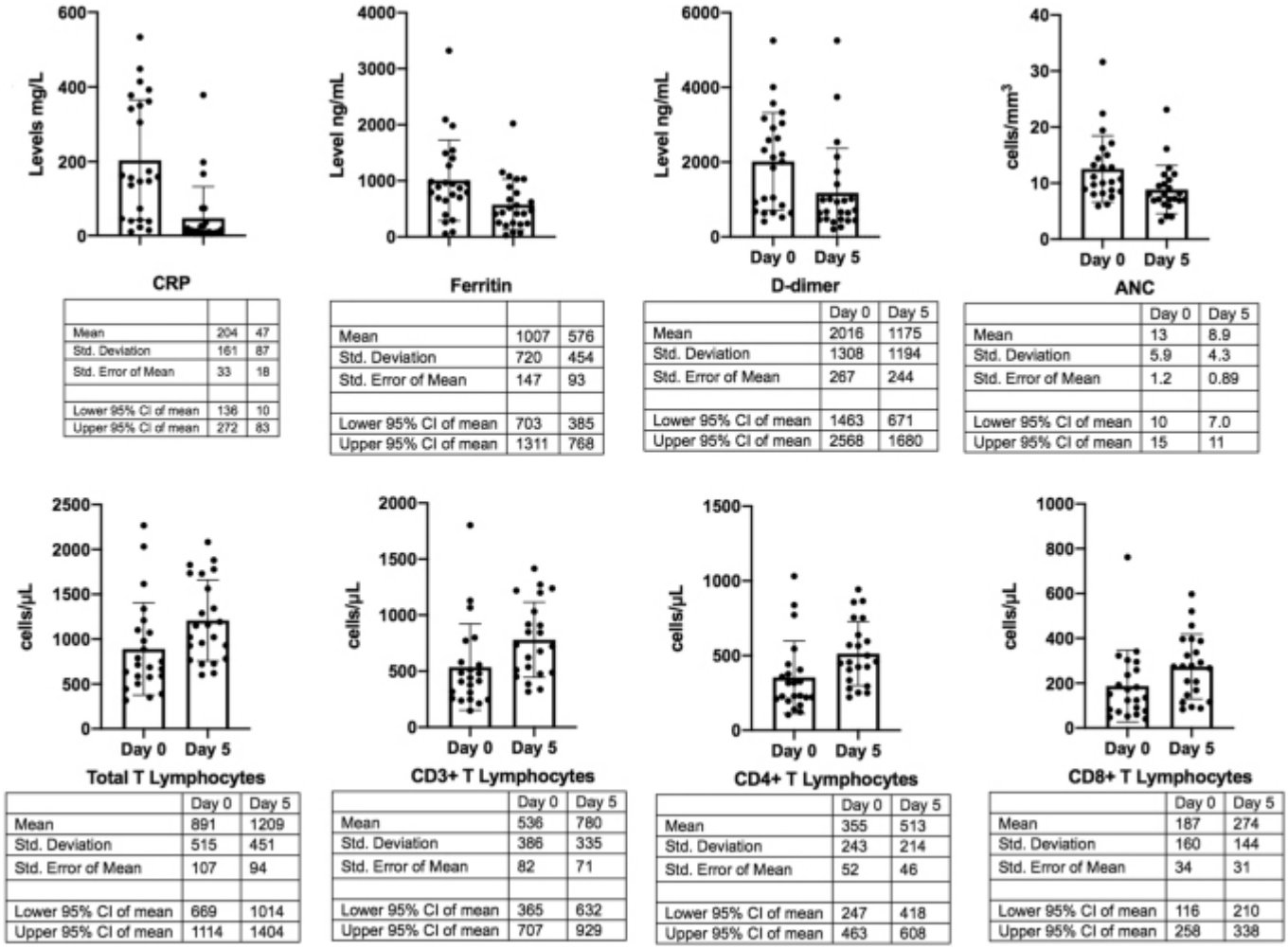
FIG. 2.

Disposition or final study clinical status, partial PaO_2/FiO_2 ratio, in addition to oxygen requirement before and after administration of ExoFlo on days 1–14. Average PaO_2/FiO_2 ratio increase was 191% ($P < 0.001$) comparing baseline with 14 days after treatment or final known value. FiO_2, fraction of inspired oxygen ratio; PaO_2, pressure of arterial oxygen.

Laboratory data

Significant reductions in levels of the acute phase reactants CRP, ferritin, and D-dimer are shown in Fig. 3. The mean reduction of CRP was 77%, the mean reduction of ferritin was 43%, and the

mean reduction of D-dimer was 42% between baseline and values measured on day 5 post-treatment. There were statistically significant reductions in absolute neutrophil count and statistically significant increases in absolute lymphocyte count including subsets staining positive for $CD3^+$, $CD4^+$, and $CD8^+$ on flow cytometry when comparing baseline with day 5 post-ExoFlo treatment.



Mean	204	47
Std. Deviation	161	87
Std. Error of Mean	33	18
Lower 95% CI of mean	136	10
Upper 95% CI of mean	272	83

Mean	1007	576
Std. Deviation	720	454
Std. Error of Mean	147	93
Lower 95% CI of mean	703	385
Upper 95% CI of mean	1311	768

	Day 0	Day 5
Mean	2016	1175
Std. Deviation	1308	1194
Std. Error of Mean	267	244
Lower 95% CI of mean	1463	671
Upper 95% CI of mean	2568	1680

	Day 0	Day 5
Mean	13	8.9
Std. Deviation	5.9	4.3
Std. Error of Mean	1.2	0.89
Lower 95% CI of mean	10	7.0
Upper 95% CI of mean	15	11

	Day 0	Day 5
Mean	891	1209
Std. Deviation	515	451
Std. Error of Mean	107	94
Lower 95% CI of mean	669	1014
Upper 95% CI of mean	1114	1404

	Day 0	Day 5
Mean	536	780
Std. Deviation	386	335
Std. Error of Mean	82	71
Lower 95% CI of mean	365	632
Upper 95% CI of mean	707	929

	Day 0	Day 5
Mean	355	513
Std. Deviation	243	214
Std. Error of Mean	52	46
Lower 95% CI of mean	247	418
Upper 95% CI of mean	463	608

	Day 0	Day 5
Mean	187	274
Std. Deviation	160	144
Std. Error of Mean	34	31
Lower 95% CI of mean	116	210
Upper 95% CI of mean	258	338

FIG. 3.

Acute phase reactants (CRP, ferritin, and D-dimer) and immune cell populations on day of treatment before IV administration of ExoFlo and on day 5 post-treatment. Mean reductions of CRP, ferritin, and D-dimer reductions were 77% ($P < 0.001$), 43% ($P < 0.001$), and 42% ($P < 0.05$), respectively. Mean reduction of ANC was 32% ($P < 0.001$); total lymphocyte count increased by 36% ($P < 0.05$) with $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocytes increased by 46% ($P < 0.05$), 45% ($P < 0.05$), and 46% ($P < 0.001$), respectively. ANC, absolute neutrophil count; CRP, C-reactive protein.

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Discussion

This prospective open-label trial on the treatment of COVID-19 demonstrated that the bone-marrow-derived product, ExoFlo, can be administered safely through intravenous infusion. The study met all of its primary endpoints. All patients were administered ExoFlo without any infusion reaction. There were no adverse effects in the immediate (<6 h), intermediate (<24 h), or delayed (<72 h) period. All adverse events occurring >72 h after administration of ExoFlo were reviewed by an independent DSMB and concluded to be unrelated to the therapeutic intervention.

All patients in cohort B met criteria for moderate-to-severe ARDS; due to their downtrending PaO_2/FiO_2 ratio, these patients were expected to require mechanical ventilation within 12–24 h before the therapeutic intervention. Only 25% (4/20) in cohort B progressed to mechanical ventilation, a critical event associated with significantly higher morbidity and mortality. Considering that mortality rates are estimated as high as 60%–79% in patients requiring noninvasive oxygen support [25,26], our preliminary findings suggest that ExoFlo may be a preventative measure against progression to invasive oxygen support and mechanical ventilation, though further studies with randomized controlled trials (RCTs) are warranted to prove efficacy. In total, 75% of cohort B (16/20) recovered, as evidenced by discharge from the hospital, demonstrating a profound reversal of disease progression and suggesting that the optimal time to administer ExoFlo is early in the cytokine storm. Overall, treatment with ExoFlo was associated with an 83% survival rate and a significant improvement in oxygenation as evidenced by a mean increase of 191% in PaO_2/FiO_2 ratio ($P < 0.001$) as well as reduced oxygen support requirements within 48–72 h. Improved PaO_2/FiO_2 ratio >200 mmHg by day 3 post-treatment was strongly predictive of eventual hospital discharge and recovery.

Interestingly, even among suboptimal responders, all clinical parameters including oxygenation and inflammatory markers showed an initial favorable response to ExoFlo, effects that peaked at days 3–4, suggesting a redose at day 3 post-ExoFlo treatment may be warranted. This is consistent with preclinical observations that circulating proteases may inactivate exosomal products, rendering a time-dependent effect in a subset of patients [15]. The significantly improved neutrophilia and lymphopenia including increased $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocytes in addition to the reduction in acute phase reactants after ExoFlo administration suggest that one main therapeutic mechanism of action may be modulation of immune dysfunction.

Overall, the strengths of this study include minimal selection bias in addition to absence of financial sponsorship as the study was prepared, designed, and implemented by independent clinicians. The primary weaknesses of this study are the absence of randomization, blinding, and the limited sample size. Furthermore, only one exosomal product, ExoFlo, was studied. Owing to the heterogeneity and complexity of exosomal products, the favorable preliminary data on safety and efficacy of ExoFlo cannot be interpreted as a class effect. Notably, bmMSC-derived exosomes were selected for this study over perinatally derived exosomes (placental, amniotic, or umbilical) because of the greater abundance of peer-reviewed research characterizing and confirming the safety profile of bmMSC-derived exosomes [24,25,27].

This is the first known clinical study to date using bmMSC-derived exosomes as treatment for any disease in an inpatient setting. Despite supporting evidence in medical literature, the clinical use of regenerative medicine has been limited to the outpatient setting, in part due to cognitive biases and lack of understanding among physicians, institutions, and regulatory agencies. This study demonstrated profound reversal of hypoxia, immune reconstitution, and downregulation of cytokine storm in patients hospitalized with severe COVID-19 following a single intravenous dose of bone marrow derived exosomes, with no adverse effects attributable to the treatment. Ultimately, the application of bone-marrow-derived exosomes may extend far beyond SARS-CoV-2 ARDS or COVID-19, spanning a myriad of inflammatory disease states, including classic ARDS, chronic obstructive pulmonary disease, sepsis, autoimmune disease, and cancer [26–34]. Further clinical studies are warranted to investigate safety and efficacy.

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Acknowledgments

The authors would like to acknowledge Benjamin Neuberg, Ira Neuberg, Olga Tarlton, AGPCNP-BC, Vikas Mukesh Shah, DO and Kory A. Imbrescia, DO for their assistance in the conduct of the study.

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Author Disclosure Statement

No competing financial interests exist.

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Funding Information

This study was supported by Drs. Vikram and Sascha Sengupta in collaboration with Christ Hospital. None of the authors were compensated for this study. Thrivewell Infusion, LLC provided acquired, commercially available product from Direct Biologics, LLC, Austin, TX, storage, medical supplies, transportation, legal resources, as well as supportive administrative and clinical personnel. No governmental funding of any kind was used to support this study.

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References

1. Gattinoni L, Coppola S, Cressoni M, Busana M and Chiumello D (2020). COVID-19 does not lead to a “Typical” acute respiratory distress syndrome. Am J Respir Crit Care Med. Advance online publication. Available at https://www.atsjournals.org/doi/abs/10.1164/rccm.202003-0817LE [PMC free article] [PubMed]

2. CNARC report on COVID-19 in critical care. (2020). United Kingdom. Intensive Care National Audit Research Centre
3. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, et al. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 8:475–481 [PMC free article] [PubMed] [Google Scholar]
4. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, et al. (2020). Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. Advance online publication. 10.1001/jama.2020.6775 [PMC free article] [PubMed] [CrossRef]
5. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, et al. (2020). Compassionate use of remdesivir for patients with severe COVID-19. NEJM. Advance online publication. 10.1056/NEJMoa2007016 [PMC free article] [PubMed] [CrossRef]
6. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, et al. (2020). Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet (UK). Advance online publication. 10.1016/S0140-6736(20)31022-9 [PMC free article] [PubMed] [CrossRef]
7. Mahévas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, Gallien S, Lepeule R, Szwebel TA, et al. (2020). No evidence of clinical efficacy of hydroxychloroquine in patients hospitalised for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a target trial. medRxiv. Online publication. 10.1101/2020.04.10.20060699 [CrossRef]
8. Alzghari SK and Acuña VS (2020). Supportive treatment with tocilizumab for COVID-19: a systematic review. J Clin Virol 127:104380. [PMC free article] [PubMed] [Google Scholar]
9. Wang X, Xu W, Hu G, Xia S, Sun Z, Liu Z, Xie Y, Zhang R, Jiang S and Lu L (2020). SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. Cell Mol Immunol 1–3. Advance online publication. 10.1038/s41423-020-0424-9 [PMC free article] [PubMed] [CrossRef] Retracted
10. Ye Q, Wang B and Mao J (2020). The pathogenesis and treatment of the “Cytokine Storm’ in COVID-19. J Infect S0163-4453(20)30165-1. Advance online publication. 10.1016/j.jinf.2020.03.037 [PMC free article] [PubMed] [CrossRef]
11. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W and Tian DS (2020). Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. Online publication. 10.1093/cid/ciaa248 [PMC free article] [PubMed] [CrossRef]
12. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, Shan G, Meng F, Du D, et al. (2020). Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 11:216–228 [PMC free article] [PubMed] [Google Scholar]
13. Liang B, Chen J, Li T, Wu H, Yang W, Li Y, Li J, Yu C, Nie F, et al. (2020). Clinical remission of a critically Ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells. ChinaXiv. Online publication. http://chinaxiv.org/abs/202002.00084
14. Metcalfe SM. (2020). Mesenchymal stem cells and management of COVID-19 pneumonia. Med Drug Discov 5:100019. [PMC free article] [PubMed] [Google Scholar]
15. Hessvik NP and Llorente A (2018). Current knowledge on exosome biogenesis and release. Cell Mol Life Sci 75:193–208 [PMC free article] [PubMed] [Google Scholar]

16. Yu B, Zhang X and Li X (2014). Exosomes derived from mesenchymal stem cells. Int J Mol Sci 15:4142–4157 [PMC free article] [PubMed] [Google Scholar]
17. De Jong OG, Van Balkom BW, Schiffelers RM, Bouten CV and Verhaar MC (2014). Extracellular vesicles: potential roles in regenerative medicine. Front Immunol 5:608. [PMC free article] [PubMed] [Google Scholar]
18. Alipoor SD, Mortaz E, Garssen J, Movassaghi M, Mirsaeidi M and Adcock IM (2016). Exosomes and exosomal miRNA in respiratory diseases. Mediators Inflamm 2016:5628404. [PMC free article] [PubMed] [Google Scholar]
19. Katsha A, Ohkouchi S, Xin H, Kanehira M, Sun R, Nukiwa T and Saijo Y (2011). Paracrine factors of multipotent stromal cells ameliorate lung injury in an elastase-induced emphysema model. Mol Ther 19:196–203 [PMC free article] [PubMed] [Google Scholar]
20. Lee JH, Park J and Lee JW (2019). Therapeutic use of mesenchymal stem cell-derived extracellular vesicles in acute lung injury. Transfusion 59(S1):876–883 [PMC free article] [PubMed] [Google Scholar]
21. Zhu YG, Feng XM, Abbott J, Fang XH, Hao Q, Monsel A, Qu JM, Matthay MA and Lee JW (2014). Human mesenchymal stem cell microvesicles for treatment of *Escherichia coli* endotoxin-induced acute lung injury in mice. Stem Cells 32:116–125 [PMC free article] [PubMed] [Google Scholar]
22. Tang X, Shi L, Monsel A, Li X, Zhu H, Zhu Y and Qu J (2017). Mesenchymal stem cell microvesicles attenuate acute lung injury in mice partly mediated by Ang-1 mRNA. Stem Cells 35:1849–1859 [PubMed] [Google Scholar]
23. Morrison TJ, Jackson MV, Cunningham EK, Kissenpfennig A, McAuley DF, O'Kane CM and Krasnodembskaya AD (2017). Mesenchymal stromal cells modulate macrophages in clinically relevant lung injury models by extracellular vesicle mitochondrial transfer. Am J Respirat Crit Care Med 196:1275–1286 [PMC free article] [PubMed] [Google Scholar]
24. Wang M, Yuan Q and Xie L (2018). Mesenchymal stem cell-based immunomodulation: properties and clinical application. Stem Cells Int 2018:3057624. [PMC free article] [PubMed] [Google Scholar]
25. Yang X, Yu Y and Xu J (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respirat Med 8:475–481 [PMC free article] [PubMed] [Google Scholar]
26. Peng F, Tu L, Yang Y, Hu P, Wang R, Hu Q, Cao F, Jiang T, Sun J, Xu G and Chang C (2020). Management and treatment of COVID-19: the Chinese Experience. Can J Cardiol [Epub ahead of print]; DOI: 10.1016/j.cjca.2020.04.010 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
27. Hicok K, Vangsness T and Dordevic M (2020). Exosome origins: why the cell source matters. Stem Cells Regen Med 4:1–4 [Google Scholar]
28. Wilson JG, Liu KD, Zhuo H, Caballero L, McMillan M, Fang X, Cosgrove K, Vojnik R, Calfee CS, et al. (2015). Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. Lancet Respirat Med 3:24–32 [PMC free article] [PubMed] [Google Scholar]
29. Lai R, Arslan F, Lee M, Sze N, Choo A, Chen T, Salto-Tellez M, Timmers L, Lee C, et al. (2010). Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury. Stem Cell Res 4:214–222 [PubMed] [Google Scholar]
30. Huang L, Ma W, Ma Y, Feng D, Chen H and Cai B (2015). Exosomes in mesenchymal stem cells, a new therapeutic strategy for cardiovascular diseases? Int J Biol Sci 11:238–245 [PMC free article] [PubMed] [Google Scholar]

31. Shao M, Xu Q, Wu Z, Chen Y, Shu Y, Cao X, Chen M, Zhang B, Zhou Y, et al. (2020). Exosomes derived from human umbilical cord mesenchymal stem cells ameliorate IL-6-induced acute liver injury through miR-455-3p. Stem Cell Res Ther 11:37. [PMC free article] [PubMed] [Google Scholar]
32. Porro C, Lepore S, Trotta T, Castellani S, Ratclif L, Battaglino A, Di Gioia S, Martínez MC, Conese M and Maffione AB (2010). Isolation and characterization of microparticles in sputum from cystic fibrosis patients. Respirat Res 11:94. [PMC free article] [PubMed] [Google Scholar]
33. Anderson MR, Kashanchi F and Jacobson S (2016). Exosomes in viral disease. Neurother J Am Soc Exp Neurother 13:535–546 [PMC free article] [PubMed] [Google Scholar]
34. Eirin A, Zhu XY, Puranik AS, Tang H, McGurren KA, van Wijnen AJ, Lerman A and Lerman LO (2017). Mesenchymal stem cell-derived extracellular vesicles attenuate kidney inflammation. Kidney Int 92:114–124 [PMC free article] [PubMed] [Google Scholar]
