

Table S1. Human and animal model sample-based studies involving IGF-signaling genes expression and action on ARDS, COVID-19 and ALI (retrieved from NCBI databases search)^{1,2}.

Patient studies¹		
Cell type-specific expression of IGFs	Disease/patients or animal model	References³
Increased IGF1 and IGF1R immunoreactivity in alveolar and interstitial macrophages, and in mesenchymal cells	Fibroproliferative ARDS vs. controls	(Krein et al. 2003)
Elevated levels of IGF1 and IGFBP3 in BALF Depletion of IGF led to enhanced fibroblast apoptosis, but not lung epithelial cells	At risk and early patients with ARDS vs. controls	(Schnapp et al. 2006)
Low plasma levels of IGF1 and IGFBP3	ARDS vs. patients in the critical care unit with severe medical illness*	(Ahasic et al. 2012)
Low plasma levels of IGF1 and IGFBP3 in non-survivors with ARDS	ARDS survivors vs. ARDS non-survivors	(Ahasic et al. 2012)
High levels of IGF1 protein and mRNA in the epithelial lining fluid/low in fibroproliferative ARDS (ARDS > 5 days), significantly higher than in early ALI/ARDS and controls	ALI/ARDS patients	(Andonegui et al. 2014)
Lower plasma IGF1 and IGFBP3 levels. Acute and chronic health factors as well as genetic factors, were associated with circulating IGF1 and IGFBP3 .	Early in clinical illness ARDS patients at ICU	(Ahasic et al. 2015)
Higher IGF1 plasma levels on day 1 and 3; Higher IGF2 plasma levels on day 1, 3 and 3 Higher IGF1R plasma levels on days 1, 3 and 7	Severe pneumonia-associated ARDS vs. controls	(Chen et al. 2016)
Lower IGFBP2 levels on day 1 and 3 Higher IGFBP4 levels on days 1 and 7	Severe pneumonia-associated ARDS vs. controls and severe pneumonia alone (days after admission)	(Chen et al. 2016)
High plasma IGF1R on day 1 at ICU as a biomarker of mortality outcome biomarker	Critical COVID-19	(Fraser et al. 2020)
Postulated role for IGF inhibition in the treatment of COVID-19-related ARDS	COVID-19 -related ARDS	(Winn 2020)
High IGF1 serum concentrations association with lower risk of mortality	(Prediagnostic) COVID-19	(Fan et al. 2021)
Low IGFALS in serum correlate with adverse prognosis (high sensitive prognostic marker) High IGBP6 and low IGFBP3 in severe disease	Severe COVID-19 (serum proteome)	(Kimura et al. 2021)
Low IGF1 associates with poor outcome in patients with Covid-19	COVID-19 vs. control	(Ilias et al. 2021)
IGF1 was lower among survivors after SARS-CoV-2 infection in elderly renal transplanted patients	COVID-19 survivors vs. non survivors	(Soliman and Sadek 2021)
Low plasma levels of IGF1 IGF1 supplementation rescues severity	COVID-19 severity	(Hazrati et al. 2022)
IGF1 , IGFBP3 , and IGFALS decline in severe and critical patients	COVID-19 severity (serum proteome)	(Wu et al. 2022)
No significant difference in serum IGF1	COVID-19 vs. controls	(Feizollahi et al. 2022)
Increased plasma IGFBP2 , and reduced IGFBP3 and IGFALS	Hospitalized acute COVID-19 vs. controls (plasma proteomics)	(Mohammed et al. 2022)
Impaired the insulin/IGF signaling pathway in respiratory, metabolic, and endocrine cells and tissues	SARS-CoV-2 infection	(Shin et al. 2022); (Kelesidis and Mantzoros 2022)
IGF1 lower levels relative to control then its levels progressively elevated concomitantly with infection severity	Hospitalized COVID-19 vs. controls	(Mohamed et al. 2023)
Downregulated plasma IGF1 , IGF2 , IGF1R , and IGF2R ; highly upregulated IGFBPs (IGFBP1 , IGFBP3 , IGFBP6) Severe cases involve IGF1R signalling	COVID-19 severity (plasma proteome)	(Iosef, Martin, et al. 2023) (Iosef, Matusa, Han, and Fraser 2024)
Plasma IGFBPs except IGFBP4 , are commonly expressed Specificity of IGFBP6 and IGFBPL1	Long COVID-19 (plasma proteome analysis)	(Iosef, Knauer, et al. 2023) (Iosef, Matusa, Han, and Fraser 2024)
High serum IGFBP2 as a severity biomarker	COVID-19 (proteome analysis)	(Mester et al. 2024)
IGFBP4 mRNA upregulated during viral amplification	Lung slices cultured <i>ex vivo</i> productively infected with SARS-CoV-2 (scRNA-seq)	(Wu et al. 2024)

Animal model studies ²		
Cell type-specific expression of IGFs	Disease/patients or animal model	References ³
mRNA expression of <i>Igf1</i> , <i>Igf2</i> , <i>Igf1r</i> and <i>Igfbp5</i> increased during injury; Protein levels of IGF1 , IGF2 , and IGF1R remained elevated until day 3 of the recovery with high abundance in alveolar type II cells	Hiperoxia lung injury in rats	(Narasaraju et al. 2006)
Deficiency in IGF1R in mice protects against oxygen-induced lung injury	Hiperoxia lung injury (72 h of exposure to 90% O ₂)	(Ahamed et al. 2005)
IGF1R blockade or deficiency improves ALI outcomes	Bleomycin lung injury/ALI in mice	(Choi et al. 2009) (Pineiro-Hermida et al. 2017)
Lung <i>Igf1</i> mRNA expression increase after bleomycin injury by Day 1, peak on Day 7 and remain higher up to day 14	Bleomycin lung injury/ALI in mice	(Choi et al. 2009)
IGF1 blockade induced mouse lung fibroblast apoptosis and IGF1 increased lung fibroblast migration via IRS2/PI3K/Akt, in vitro.	Primary mouse fibroblasts	(Choi et al. 2009)
IGF1 promotes lung wound healing/anti-inflammatory M2 macrophage phenotype	LPS-induced ALI in mice	(Ionescu et al. 2012)
IGF1R blockade decreased hyperoxia lung injury	Hyperoxia lung injury in mice	(Kim, Chow, Gill, and Schnapp 2012)
IGF1 plays a synergistic fibroproliferative role in lungs in the presence of TGFβ1	Intratracheal transduced mice with IGF1 and Tgfβ1 expressing adenovirus	(Andonegui et al. 2012)
IGFBP5 and IGF1 expression in the type II AECs play a key role in lung injury	Bleomycin lung injury/ALI in rats	(Kotarkonda, Kulshrestha, and Ravi 2017)
Inhibition of IGF1R reduces necroptosis-related markers and attenuates ALI	LPS-induced ALI in mice	(Lee et al. 2018)
Upregulated expression of IGF1 in H1N1 influenza A virus infected mice. Overexpression of IGF1 aggravated viral inflammatory response, whereas inhibition of IGF1R reduced such inflammatory response	Acute H1N1-mediated ALI in mice	(Li et al. 2019)
Recombinant human IGFBP3 attenuates LPS-induced ALI in mice Increased IGF expression in BALF and lungs of ALI mice and downregulation of IGFBP3	LPS-induced ALI in mice	(Kang et al. 2020)
IGF1 upregulation in BALF and lung tissues of ALI mice; this increased IGF1 was mainly derived from alveolar macrophages mediated by TGFβ production by alveolar epithelial cells	Lipopolysaccharide-induced ALI in mice	(Mu et al. 2020)
IGF1 and BTP2 dual therapy in the lungs normalize primary inflammatory mediators	LPS-induced ALI in mice	(Munoz et al. 2021)
Upregulation of IGF1 and downregulation of IGF1R	Bleomycin lung injury/fibrosis in mice	(Kheirollahi et al. 2022)

¹ In case of patients studies the search terms in NCBI/Pubmed and NCBI/GEO databases were: "ARDS and IGF", "COVID-19 and IGF", "SARS-CoV-2 and IGF" and "human and ALI and IGF".

² For animal models of ALI the search terms in NCBI/Pubmed and NCBI/GEO databases were: "bleomycin and IGFs and mouse models" and "acute lung injury and IGFs and mouse models".

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