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Accelerated hyaluronan concentration as the primary driver of morbidity and mortality in high-risk COVID-19 patients: with therapeutic introduction of an oral hyaluronan inhibitor in the prevention of "Induced Hyaluronan Storm" Syndrome

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Abbreviations: COVID-19, novel coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HA, hyaluronic acid or hyaluronan; IHS, induced hyaluronan storm; CSS, cytokine storm syndrome; SEB, staphylococcal enterotoxin B

Word count: 2,714

"You may take notes for 20 years, from morning to night at the bedside of the sick, upon the diseases of the viscera, and all will be to you only a confusion of symptoms...a train of incoherent phenomena. Open a few bodies and this obscurity will disappear." - Marie-François-Xavier Bichat (1771–1802), "The Father of Histology"[1].

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Abstract

To date, the fundamental drivers of the morbidity and mortality in COVID-19 remain uncertain. Clinicians worldwide appear to be at a loss to know how to prevent and treat the severe respiratory distress in these patients effectively. Consequently, the fundamental mechanisms leading to death in high-risk patients need to be discovered and addressed with urgency. The post-mortem autopsy remains an essential part of both discovering the cause of death in a particular individual, but also in advancing the science and treatment of disease, especially in the case of novel pathogens such as SARS-CoV-2[2]. The goal of an autopsy is to discover the cause of death (COD) using a macro/microscopic investigation. Because lung weight is often affected by the cause of death and the last breath occurs very near if not now of death, the evaluation of the lungs is one of the starting points of any COD investigation[3]. A comprehensive search was performed to systematically review all reported autopsy findings in COVID-19 patients with respect to lung weights and histologic findings. We then compared these findings with the results of a targeted literature review of hyaluronan in relationship to acute respiratory distress syndrome (ARDS). In total, data from 38 autopsies were identified. From this group, 36 autopsies of COVID-19 patients were selected for detailed review and statistical analysis. The average lung weight of those who were determined to have died as a result of SARS-CoV-2 was 1994g approximately 3.7 times the normal lung weight. Hyaline membranes were consistently identified on histologic sections. A review of the literature reveals that markedly elevated lung weights and hyaline membranes and have been associated with the pathophysiology of ARDS since 1967. However, the key role key of hyaluronan in driving the morbidity and mortality of the condition has heretofore not been fully recognized. We propose that the induced hyaluronan storm syndrome or IHS, is the model that best addresses the heretofore perplexing respiratory failure that is the proximal cause of death. An aggressive

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research effort should be undertaken to discover why the majority of individuals who are exposed to the virus are minimally symptomatic, while a minority of high-risk individuals rapidly progress to respiratory failure and death.

Keywords Systematic review; COVID-19; SARS-CoV-2; Hyaline Membrane; Hyaluronan; Acute Respiratory Distress Syndrome; ARDS; Autopsy; IHS; Induced Hyaluronan Storm Syndrome; COD; Cause of Death

Introduction

To date no coherent model has emerged to explain, prevent, or treat the rapid respiratory failure that is the proximal cause of death in a minority of 2019 novel coronavirus (2019-nCOV; SARS-CoV-2; COVID-19) patients. Similarly, this remains true for the acute respiratory distress syndrome (ARDS) first described by Ashbaugh in 1967[4] seen in the severe acute respiratory syndrome (SARS) outbreak in 2002, and the Middle East respiratory syndrome (MERS) in 2012. Clearly, a small subset of infected individuals rapidly progress, often in a few hours to a few days, from initial symptoms of fever and dyspnea, to full-blown respiratory failure requiring mechanical ventilation, while others remain essentially asymptomatic. Once placed on a ventilator, the death rate has been reported to be between 37 to 62 percent and up to 80 percent depending on age and other risk factors[5]. Currently, the explanation offered to explain this rapid chain of events has been the cytokine storm syndrome (CSS)[6,7]. However, this model is lacking in some respects, and does not readily lead to a broad based hypothesis and treatment protocol that can be tested immediately. Using a systems biology framework[8], we conducted a comprehensive review of autopsy reports relating to SARS-CoV-2 deaths, and reviewed the literature concerning hyaluronan with respect to acute respiratory distress syndrome (ARDS). We found that there is a consistent and statistically significant increase in the reported lung

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weights at autopsy in confirmed SARS-CoV-2 victims. Most significantly, in the first report of two complete autopsies in SARS-CoV-2 in the English language literature, the observed lung weight of a victim with a positive nasopharyngeal and bilateral lung parenchymal swab, by rRT-PCR for SARS-CoV-2, weighed 2,452g - approximately 4.6 times the normal adult lung weight. These lungs were described at autopsy as a "bag of water" (personal communication)[9]. In sharp contrast, and most importantly, a 42-year-old obese man was determined to have died with SARS-CoV-2 but not because of SARS-CoV-2. At postmortem examination, the nasopharyngeal swab tested positive for SARS-CoV-2 but there was a negative lung parenchymal swab, with normal lung weights and findings of acute bronchopneumonia.

Modig and Hällgren in 1989, elegantly demonstrated that hyaluronic acid (HA) can be induced within minutes in alveolar fluids and leads to a dose dependent reduction in pulmonary oxygenation index, PaO_2/FaO_2. They further demonstrated up to an 82 times increase in alveolar HA concentration in ARDS patients compared to controls. Stating that "hyaluronic acid is the most powerful water(edema)-binding substance in the body", they put forth a "humoral" and "biochemical-physiological" hypothesis of ARDS[10]. Recently, others have detailed the central role of HA in human respiratory disease, in which viral infections lead to marked and rapid increase in HA concentrations[11]-[13]. This may serve to confirm the unique cause of death in the postmortem examination, aforementioned by Barton et al., whereby the super-normal outpouring of HA over a short time interval within the confined space of the human chest cavity leads to acute respiratory distress. We propose to define a new model of the induced hyaluronan storm (IHS) syndrome, as the most comprehensive, specific, and actionable paradigm to frame and address the global COVID-19 crisis and specifically, to prevent death in high-risk groups.

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In 2013, McKallip, et al. reported an *in vitro* and *in vivo* model of ARDS stating that "targeting hyaluronic acid synthesis might be a novel target for the treatment or reduction of induced lung injury". Using an elegant combination of cell based and murine studies, they demonstrated that it was possible to profoundly suppress the production of HA by inhibiting the three isoenzymes of HA synthase (HAS-1, HAS-2, and HAS-3) with 4-methylumbelliferone (4-MU)[14].

A follow up study by the same group went on to show that 4-MU reduces the expression of HAS-1, HAS-2, and HAS-3, and reduced levels of HA in the lungs of Staphylococcal enterotoxin B (SEB)-exposed mice and that 4-MU treatment yields a reduction in SEB-induced lung permeability and reduced cytokine production[15].

Bray et al. in 1991 demonstrated in a bleomycin-induced lung injury model, maximal HA content was reached after seven days and was 14.6 times the normal value[16]. More recently, Reeves et al. in 2020, showed that human lung fibroblasts (HLFs) treated with viral mimetic polyinosine-polycytidylic acid, a Toll-like receptor 3 agonist, encourages the accumulation of HA-rich extracellular matrix (ECM) and enhances monocyte and lymphocyte binding. It was shown that the activity of mast cells (innate immune cells), particularly in acute respiratory infections such as RSV, can lead to the formation of a HA-enriched ECM. This further emphasizes that RSV infections of HLFs encourage inflammation via HA-dependent mechanisms that enhance mast cell protease expression through direct contact with the ECM[17]. Furthermore, HA and its various degradation products *in vitro* have been shown to be a significant contributor to the immunomodulatory functions of the ECM in both acute and chronic respiratory diseases.

In 2015, Paul Bollyky, M.D., PhD. and Nadine Nagy PhD. et al., researchers at Stanford, extensively reviewed the use of 4-MU in both animal and human studies. This was

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accomplished by investigating its mechanism of action, pharmacokinetics, and safety, with respect to cancer and autoimmunity. These researchers reported eight human studies dating back to 1978 involving HA and cancer. They concluded that 4-MU has the potential of becoming a long-term adjunctive therapy for myriad indications[18].

Methods

Study Type A systematic comprehensive review of COVID-19 autopsy reports and scientific literature using key search terms.

Inclusion Criteria The inclusion criteria of this study were: COVID-19 autopsy reports; search results involving the selected terms COVID-19, Autopsy, Hyaluronan, Hyaluronic Acid, ARDS.

Exclusion Criteria Studies were excluded if they lacked (i) corresponding outcome parameters or research data or (ii) did not have available full text.

Search Strategy We conducted a targeted systematic review following the PRISMA flow diagram methodology. J.A.A. and M.A.M. systematically searched the electronic databases, PubMed and Scopus, for eligible reports following the PRISMA methodology (flow diagrams and search terms are listed in Figure 2). We included full reports with original data and applied no exclusions based on language. The search deadline was on May 27, 2020.

Data Extraction The elements extracted included sample size, location, measurement indicators of lung, spleen, liver, and circulatory systems. Literature was reviewed independently by two researchers (J.A.A. and M.A.M.). Autopsy reports were also screened for pre-existing conditions (n = 2 subjects with lung cancer and n = 1 non English literature cases were excluded). The primary outcome of interest was SARS-CoV-2 autopsy results with reference to lung weights and presence of hyaline membranes. Mechanisms related to HA's role in ARDS pathology were selected for detailed analysis.

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Data Collection and Quality Assessment Relevant data elements were identified from each publication and recorded in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and Zotero (George Mason University, Fairfax, VA, USA). All citations extracted from the PubMed or Scopus electronic databases were deemed to be of sufficient scientific quality.

Data Synthesis and Analysis We summarized the autopsy findings and compared the association between each outcome from the relevant studies. Further collating these results with citations related to HA and ARDS. These findings were compiled in an outcome status report in the form of a supplementary table, listing the significant findings from each case study. Statistical analysis was carried out with respect to both COVID-19, ARDS, and normal lung weights.

Results

Search Results We identified 106 eligible publications after removing duplicates (Figure 2). Of these, 95 publications were excluded after screening titles and abstracts. Of the remaining, 9 publications were reviewed with full-text reads, two publications that did not meet the inclusion criteria were excluded, leaving 7 publications for the analysis. The final autopsy count as of May 27th, 2020 was 36 cases. Biological factors such as age ranged from 31 to 87, with an average age of 57. All publications were considered sufficient scientific quality and the anatomic and histologic findings in SARS-CoV-2 reports were collated and further analyzed. Case 1, (Barton) with bilateral lung parenchymal swabs positive by rRT-PCR for SARS-CoV-2 had a lung weight of 2,452g - approximately 4.6 times the normal adult lung weight and showed the presence of hyaline membranes and bilateral diffuse alveolar damage. Case 2, (Barton) autopsy revealed positive nasopharyngeal but negative bilateral lung parenchymal swabs by rRT-PCR for SARS-CoV-2, lung weight was documented at a normal 1191g.

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Statistical Analysis Average lung weights[3, 9, 21-25] were plotted on MATLAB (MathWorks, Natick, MA, USA) and Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). A one-way Analysis of Variance (ANOVA) coupled with a post-hoc analysis was performed using a Tukey Honestly Significant Difference (HSD) test. Namely, a Tukey HSD test was performed to adjust the p-values and indicate group statistical significance; however, note that a Tukey HSD test requires a studentized range distribution. This statistical model was performed using a 95% confidence interval between the groups. Due to the limited number of lung weights in confirmed COVID-19 IHS- victims, we cannot determine a final p-value at this point. One COVID-19 IHS- case was recorded with a combined lung weight of 1191g[9].

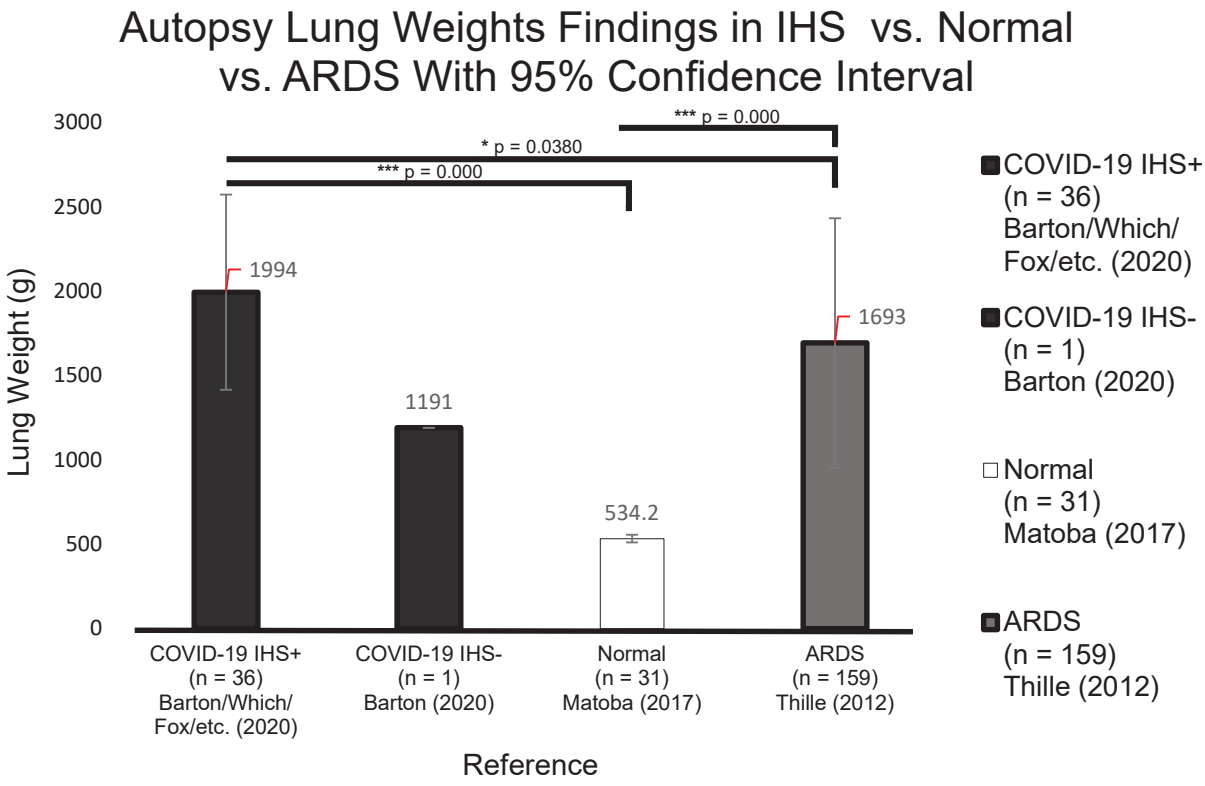

Figure 1. Statistical analysis of lung weights in IHS±, normal, and ARDS autopsies. A one-way ANOVA was performed followed by a post-hoc Tukey HSD. Because SARS-CoV-2 autopsy lung weights were limited, a small sample size was analyzed for IHS+ victims.

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Discussion

We employed a systems biology[8], rather than a reductionist approach, to better characterize and understand the mechanisms associated with the morbidity and mortality associated with COVID-19. We propose that a hyperacute rise in HA concentration is the key driver of morbidity and mortality in SARS-CoV-2 patients. The induced, sudden, and overwhelming increase in HA concentration, directly leads to a fatal accumulation of water in the lung parenchyma, overpowering the body's defense mechanisms, causing rapid asphyxia and death, similar to drowning. No interventions directed towards the down stream effects of this massive accumulation of HA, and requisite water, can prevent the consequences of this singular hydrostatic event.

Under appreciated and neglected since the first description of the clinical features of ARDS based on careful autopsy results in 1967[4], the morphologic and spacial implications of the sudden outpouring of HA and it's sequestration of water in the alveolar environment, has not been fully appreciated and specifically addressed. Unfortunately, the historical focus has been centered on the down stream consequences, and not the critical and key physical dimensions and spacial aspects of a large volume of accumulated and misplaced water in the lung. Essentially the lung parenchyma, as a direct consequence of massive increases in HA, rapidly becomes saturated with water. Occurring within minutes, these shifts in water, as a direct result of a variety of injuries, and in this case, yet unknown and particularly lethal aspects of the SARS-CoV-2 infection, result in ARDS and require ventilation within hours.

Critically, with respect to the above mechanism, it follows that conventional treatment with positive pressure ventilation, and anti-inflammatory medications can not overcome the physical effects of water saturated lung tissue.

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These findings, and numerous others, all suggest that treatments targeting the production of HA may be life-saving in the present pandemic. The beneficial effects of 4-MU in patients that are currently on ventilators, and certainly in symptomatic patients who have not crossed the line into respiratory failure, is strongly suggested by the extant literature.

Fortunately, evidence exists that 4-MU, which has been readily available in European Union as an over the counter product, called Cantabilin®, with a current marketing authorization via the Italian Medicines Agency (AIC no. 02130002) might be available for compassionate use.

Given the weight of these findings as well as the long track record of the safe use of 4-MU, and particularly the pressing need and current lack of a specific treatment for the COVID-19 ARDS phenotype, we propose that those on the front lines consider immediate use of 4-MU under compassionate use guidelines.

The work of Paul Bollyky, M.D., PhD. and Nadine Nagy PhD. et al., would suggest that 800 mg by mouth three times per day at first sign of infection in confirmed high risk patients might be a reasonable initial dose[18]. These findings provide a rationale for studying the use of 4-MU in COVID-19 induced hyaluronan storm in a prospective, double-blinded clinical trial in high-risk patients. We strongly recommend these trials starting at the earliest time frame possible, and encourage readers to recommend specific protocols for doing so. It is known that drugs have unanticipated and unwanted side effects, therefore precautions must be taken in the clinical application of this, or any other compound for the treatment of COVID-19. Certainly, 4-MU should only be used under the direct supervision of skilled physicians.

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Conclusion

COVID-19 disease has resulted in a disastrous pandemic of enormous consequences, the likes of which have not been seen in modern times. We propose that the induced hyaluronan storm syndrome (IHS), is the model that best addresses the heretofore perplexing respiratory failure that is the proximal cause of death in a minority, but ever rising number, of patients. We encourage researchers and clinicians to put our model to the test, and expand upon our early understanding of this disease. In addition to treating and preventing IHS in currently infected individuals now; an aggressive research effort should be undertaken to discover why the majority of individuals who are exposed to the virus are either minimally or asymptomatic, while a minority of high-risk individuals rapidly progress to respiratory failure and death. The answer to this question will have profound implications for our fundamental understanding and approach to disease, and for the individuals and institutions charged with the management of this and future threats to global health and well-being. Foundations have been shaken, and the future will be profoundly shaped by these historic events, as history has been shaped by similar events in the past. Let us hope our collective responses are enlightened, cooperative, and well reasoned.[20] Future directions include the reporting of further IHS± SARS-CoV-2 lung weights and performing additional autopsies on SARS-CoV-2 victims. We recommend the measurement of HA in serum as a potential indicator of IHS status.

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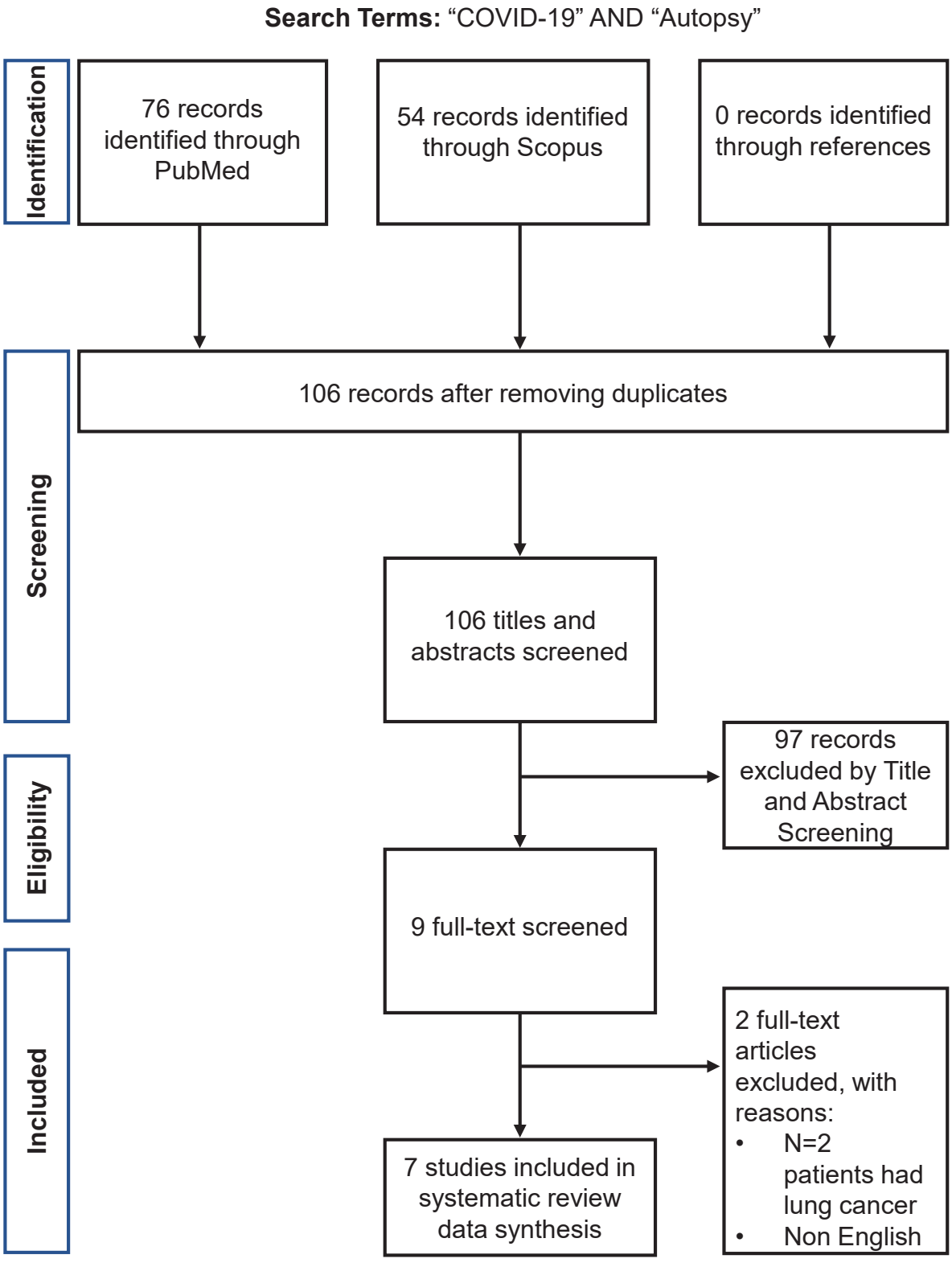

Figure 2. Flow chart of study selection

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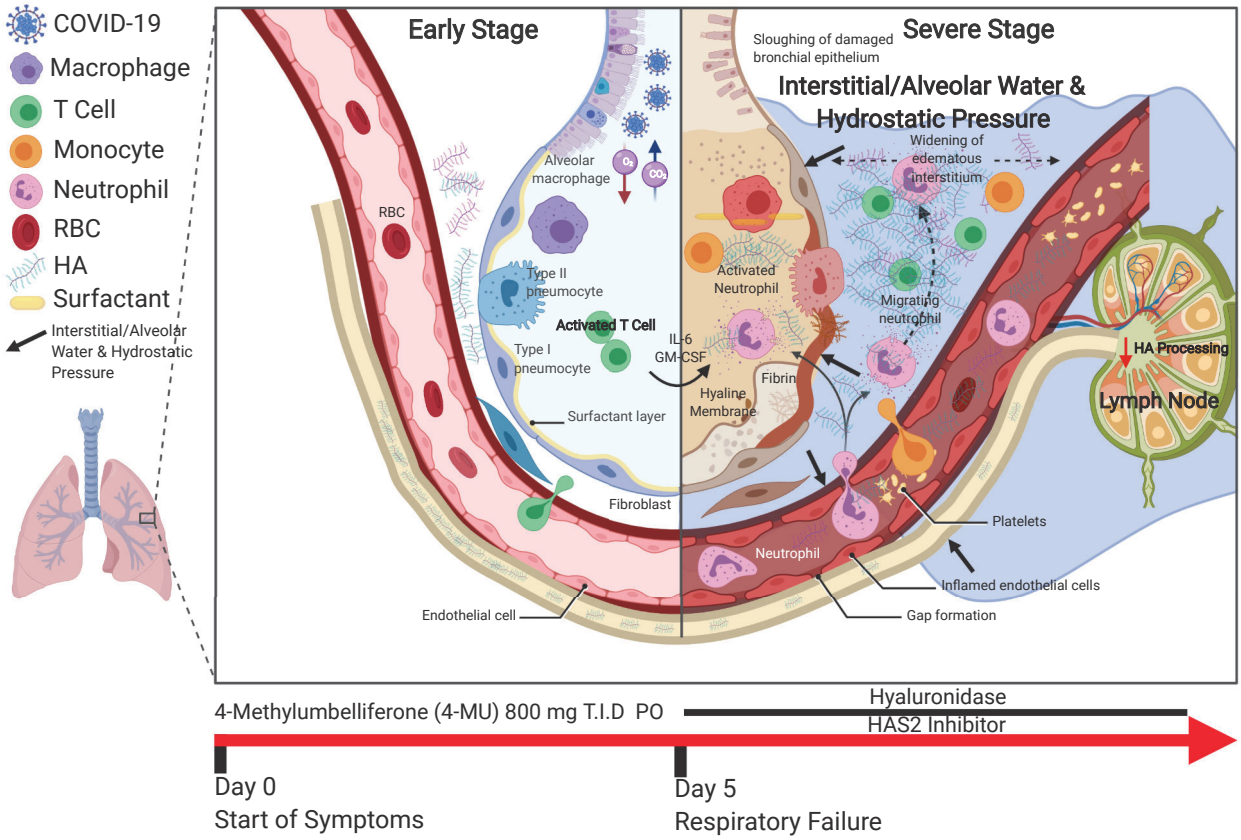

Figure 3. Schematic of the progression of SARS-CoV-2 infection and potential interventions. Inhibition of hyaluronan synthase and elimination of hyaluronan should be considered.

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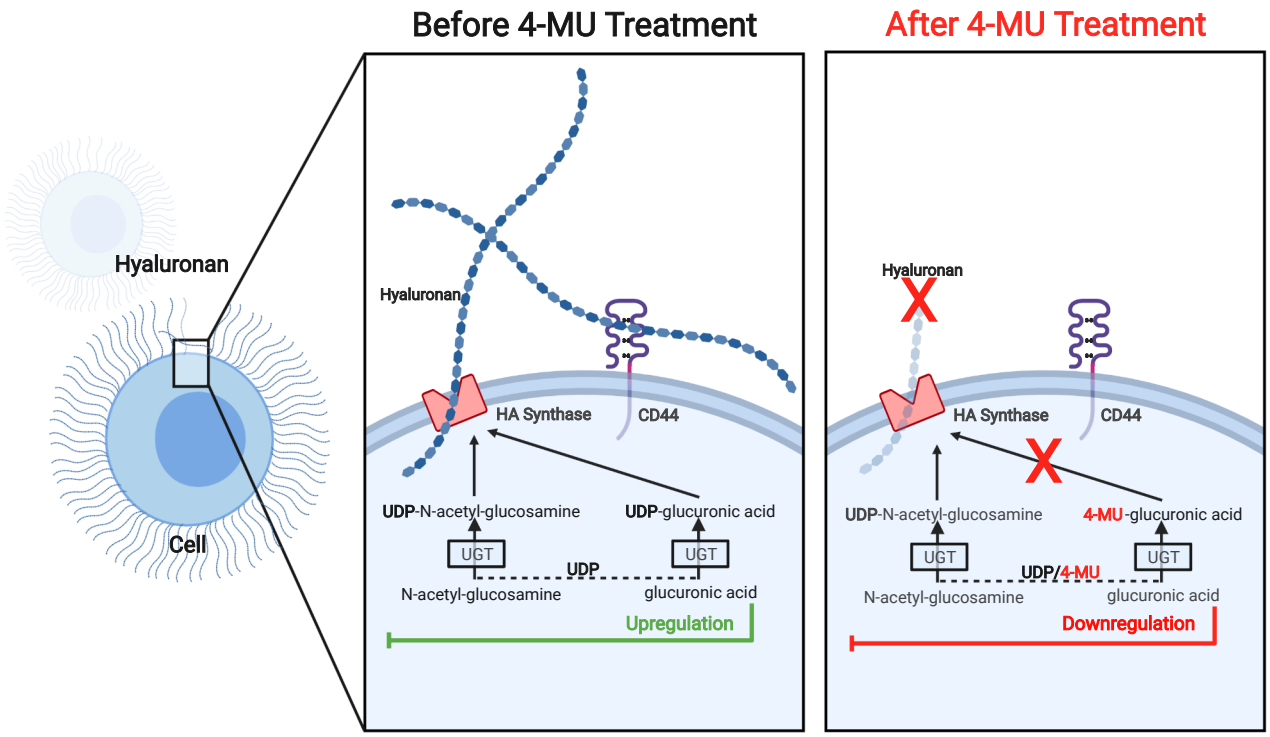

Figure 4. Schematic of the 4-MU treatment and biochemical pathway. Inhibition of hyaluronan synthase and elimination of hyaluronan should be considered.

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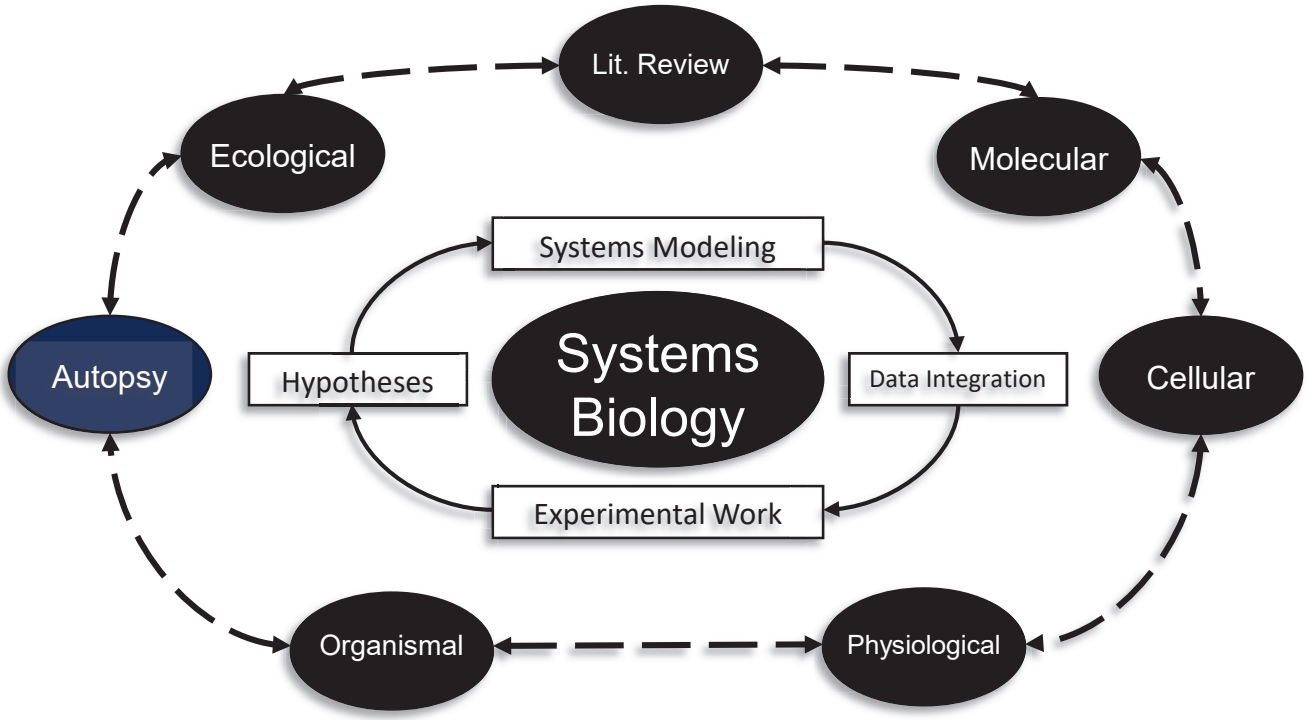

Figure 5. Theoretical framework outlining the elements of a system biology, in contrast to reductionist, approach to complex disease states. Note the inclusion of autopsy as an integral component of this dynamic network.