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The Cytokine Storm and Pre-Cytokine Storm Status in COVID-19-A Model for Managing Population Risk for Pandemics and Chronic Diseases

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Abstract

The emergent outbreak of disease from SARS-CoV-2 (COVID-19) has caused a global pandemic and highlights a need for a more proactive approach to medical diagnostics and care delivery since immunocompromised individuals and those with preexisting condition are subject to extraordinarily high morbidity and mortality. Acute Respiratory Distress Syndrome (ARDS) and multiorgan dysfunction are among the leading causes of death in critically ill patients with COVID-19. Elevated inflammatory cytokines, noted in COVID-19 cases, suggest that a cytokine storm, also known as cytokine storm syndrome (CSS), may play a major role in the pathology of COVID19. This pathway suggests reaction by the innate immune system as the primary physiological defense mechanism against the virus. Our and emerging data indicate that those most vulnerable to mortality from COVID-19, including immunocompromised individuals and those with preexisting disease diagnoses, present with elevated cytokines at baseline and this burden likely contributes to adverse outcomes. Reactive treatments with immunosuppressant anti-inflammatories to reduce mortality from COVID-19-induced CSS is controversial but may offer a solution to reduce mortality from the latest stages of CSS. There is an urgent need for better risk characterization among populations, during a pandemic, to facilitate more targeted policy decisions based on vulnerability.Novel interventions, both proactive and reactive, to treat COVID-19-induced CSS, discussed here, may shorten the duration of any lockdown or requirement for social distancing. Here we discuss the pathogenesis of Severe Acute Respiratory Syndrome (SARS)-induced CSS, compare the CSS in COVID-19 with that in SARS and Middle East Respiratory Syndrome (MERS) and discuss physiological markers elevated in CSS. We illustrate interventions used to mitigate risk on the early CSS continuum that function as "vaccines" for innate, rather than adaptive, immunity. We propose a biphasic approach to moderate the severity of this and future viral-based pandemics. We also posit that the diagnostics and interventions used to mitigate pandemics may also be a model for a new healthcare approach when applied for the measurement and reduction of chronic disease burden and immunocompromised status. The approaches include measurement of preexisting risk by accurately determining pre-cytokine storm status on a population basis, similar to the measurement of prediabetes to forestall diabetes. Part 2 is the reversal of pre-cytokine storm status, proactively, using a broad array of interventions.

Keywords: Acute Respiratory Distress Syndrome; Immunity; SARS-CoV-2 (COVID-19); Vaccines; Virus

Introduction

Cytokine Storm Syndromes (CSS) are a group of disorders representing a variety of inflammatory etiologies with the final common result of overwhelming systemic inflammation, hemodynamic instability, multiple organ dysfunction, and potentially death. This clinical constellation is caused by the generation of extreme amounts of inflammatory mediators resulting from unchecked innate immune activation and amplification against a rapidly proliferating infectious antigen. In the context of pandemics, the initiating factors leading to the end state of CSS are derived from infectious origins and pre-susceptibility loosely defined as "immunocompromised" status and being afflicted with preexisting chronic diseases.

Newly emerging and re-emerging viral threats have continued to challenge medical and public health systems that apply last-stage interventions resulting in exorbitant multifactorial costs to both individuals and societies [1]. The influenza virus is a main cause of those threats and is responsible for millions of severe cases and 250 000-500 000 deaths each year [2]. The scenario can be even worse during a pandemic year. The most virulent influenza, the 1918 H1N1 Spanish flu, infected large global populations leading to a 2% total mortality in those infected [3]. Subsequently, the H2N2 Asian influenza of 1957, the H3N2 Hong Kong influenza of 1968, and the H1N1 pandemic influenza of 2009 reported lower mortality rates in the range of 0.2% or less. Novel modern viruses including H5N1, H7N9, and H10N8 crossed the species barrier to cause human morbidity and mortality [4,5]. These infections, in humans, are accompanied by a raging pro-inflammatory response often without concomitant anti-inflammatory adaptation, the combination of which is called a 'cytokine storm' [1].

COVID-19 is the newest member of the Coronaviridae family of viruses and is the third coronavirus crossing animal species barriers to infect human populations. The previous two members of the family are the Severe. Acute Respiratory Syndrome Coronavirus (SARS-CoV), emerging in 2002, and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), in 2012. All can cause severe, even fatal, sudden acute respiratory syndrome or severe cardiopulmonary distress [6]. The SARS-CoV-2 may also be creating a systemic hypoxic environment by inhibiting the functioning of Heme [7].

COVID-19 attests to the high mutational capacities of coronavirus family members. By extending their reservoir range to include other animal species, by delaying the onset of symptoms while maintaining infectivity, and by further affecting human-to-human transmission and expanding infection routes to include droplet, oral-fecal, and body fluids modes, SARS viruses have great capacity to create epidemics and pandemics [8]. As with many viruses, coronaviruses have complex host invasion, replication, and transmission cycles. A crucial replication phase, known as the viremic phase, involves the explosive reproduction of viral particles and virions, exiting from infected and dying host cells, expelling billions of viral precursors into many types of bodily fluids leading to sudden and massive infiltration of any organ, challenging and overwhelming innate immunity leading to CSS and sepsis [9].

Based on early reports on COVID-19, the cytokine profile of critically ill patients shows higher concentrations of granulocyte-colony stimulating factor, interferon gamma-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α and tumor necrosis factor α and that their levels are linked to severity of disease [10]. Another study from China reported that increased expression of interleukin (IL)-2R and IL-6 in serum appears to predict the severity and prognosis of patients with COVID-19 [11]. Inflammatory infiltrates with lymphocytes were found in lungs based on pathological examination along with overactivation of T cells [12].ACE2 acts as a guardian to inactivate B1 receptors on endothelial cells in the lungs without which there is an enhancement of local immune cell influx and proinflammatory cytokines leading to damage [13].

In the event of any disease, its severity is the result of the interaction between causal factors and host resistance [14]. This includes essentially all infectious diseases. A matrix of responses, rather than a single consistent response, is possible. In immuno-compromised individuals, the response to even mild causal factors may be severe whereas in individuals with strong immunity, the response to severe causal factors may be mild or even non-detectable. In those with compromised immunity, hyper reactivity is often observed. For example, for infections caused by the Spanish flu or the H5N1 influenzas virus, an excessive inflammatory reaction occurred in many and may have been the cause of death, not the action of the infection itself although it,along withphysiological health, wasthe precipitating feature[15].

Cytokine Storm and Chronic Diseases

Cytokine storms occur in various illnesses. Bacterial infections that are severe and systemic, causing sepsis, for example, may trigger a storm leading to cardiovascular system failure. Elevated cytokines are present in cardiovascular diseases. In heart failure, this connection was first reported in 1990 [16]. Subsequently there have been vast publications on elevated inflammatory mediators and acute decompensated heart failure. Mann explains that both innate and adaptive immune responses are activated in the heart in response to tissue injury that results from pathogens or environmental injury [17]. In the Jupiter study, the meager benefit of statin drugs to prevent myocardial infarction was attributed to their action on inflammation as measured by C-reactive protein [18]. In fact, the anti-inflammatory action of statins may be due to the documented antimicrobial action of these drugs [19]. Cytokine storms follow tooth extractions. Dento-alveolar surgical procedures in inflamed and hyper-vascularized tissues could lead to an excessive endotoxin and cytokine release into the blood circuit resulting in unexpected fever, hypotension or dizziness. Different factors such as gram-positive toxins, fungal toxins or glycosylphosphatidylinositol are known to stimulate a cytokine release [20]. Owing to inflammation vascular disease connection, and the broad-based impact of COVID-19 on multiple organ systems, a role of infection across multiple chronic conditions, driven through the vascular system, that eluded causal determinations and solutions in the standard of care, must be considered. A keyword search of PubMed for an association

between infection and various chronic diseases shows a remarkable correlation when charted against early reports of COVID-19 death rates and preexisting disease, **Figure 1**[21]. If this association can be shown to have a causal effect as well, then the measurement of pre-cytokine status, and the resolution thereof, may be an appropriate future path for medical diagnosis and intervention across a broad range of common prolific chronic diseases.

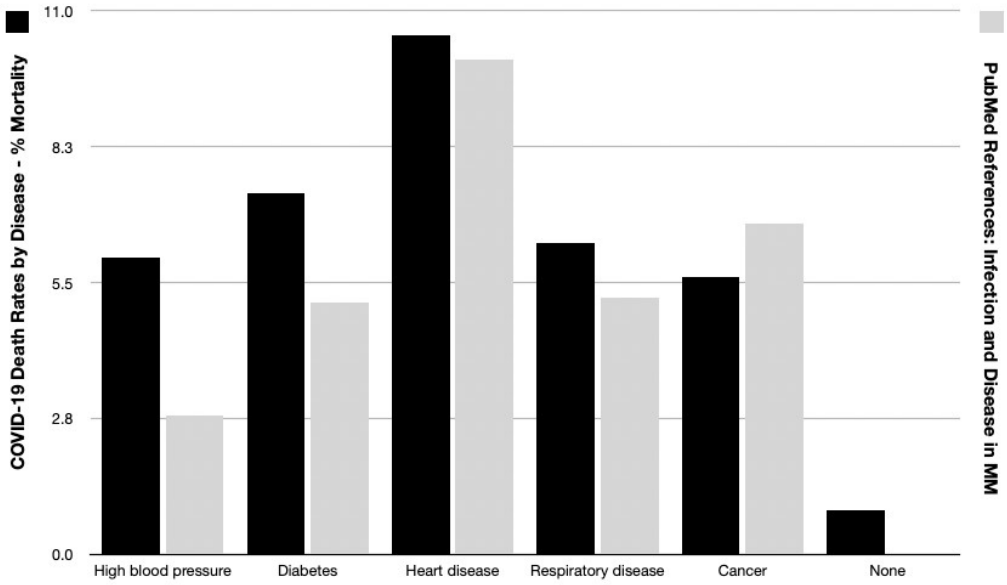

Figure 1: Mortality rate for COVID-19 with pre-existing disease by percent (black) and number of references in PubMed with an association between the disease and the term "infection" (grey).

Physiology and Biomarkers in a Cytokine Storm

In consideration of the value of various tests for pandemic disease, PCR and antibody tests have limitations. Positive PCR assay for SARS-CoV-2 does not imply disease or contagiousness. Variables in sample site quality and in the time, energy, and trained personnel required to run these tests, all of which limit scalability, contribute to ambiguity. Antibody testing looks for an adaptive immune response and the phase and magnitude of the infection. These tests provide little information on projected outcomes as healthy people are much less likely to die compared to unhealthy or older people[22]. Physiological health, the main concern of practicing clinicians, is not articulated through these tests. Further, the main cause of death appears to be CSS which is driven by innate, not adaptive immunity. Thus, antibody testing is only a portion of the risk story. Validated data on severe respiratory viral diseases and the correlation between mortality, immunocompromised status and existing chronic conditions in infected individuals indicate that a broad set of blood-based biomarkers may best serve to stratify risk and to set policy on containment strategies in populations [23,24]. Currently, policy is being established with an incomplete set of evidence. In vivo blood biomarker analysis offer considerable opportunities for individual and population risk measurement. These tests afford fast analytical turn-around time, quantitative measurement, accessibility, serial monitoring and ready availability. In some instances, rapid and continuous monitoring is available.

CSS involves a complex interplay of various cytokines, some of which are more piqued during disease. Patients with COVID-19, SARS or MERS present with distinct cytokine profiles, **Table 1**. In addition, cytokines are considered acute-phase reactants, the half-life of which may cloud interpretation of risk status depending upon the timing of the disease onset, its severity, and timing of sample acquisition [25]. However, variations in half-lives can also be applied as a clinical tool in determining the stage of an inflammatory condition and, by extension, potential for a cytokine storm, risk, and poor outcomes. Evaluating health status, through evaluation of multiple biomarker, coupled to frequent testing and regression analysis (for more accurate assessment of disease progression or regression), is an approach seeing more wide acceptance [26,27]. Current health assessments are focused on acute health status and use a very limited set of markers to determine chronic health. Using multiple biomarkers in patient workup improves both precision and accuracy of a diagnosis or risk. COVID-19 is teaching us that risk may be more important compared to a subjective diagnosis of an indication based on limited physiological data. A common example is the use of both the HbA1C and fasting glucose test for diabetes and risk. While the glucose test provides an instantaneous value, the HbA1C provides an average surrogate value for glucose over a 120-day period leading to better patient characterization. However, although the underlying disease is insulin resistance, a fasting insulin test is seldom used. Up or down arrows indicate higher or lower levels versus normal controls, respectively. Abbreviations: NS; no significant change versus normal controls, IL: interleukin, IFN-γ: interferon γ, IP: induced protein, MCP: monocyte chemoattractant protein, TNF-α: tumor necrosis factor α. Reprinted by permission [28].

Cytokines	COVID-19	SARS	MERS
IL-6	↑ in some or in severe cases	↑	Unknown but ↑ in severe than in mild cases
IL-2	↑	↑ or NS	NS
IL-1β	↑	NS	Unknown
IL-8	↑	↑	Unknown
IL-17	↑	Unknown	↑
IFN-γ	↑	NS	↑
TNF-α	↑	NS	↑
IP10	↑	↑	Unknown but ↑ in severe than in mild cases
MCP-1	↑	↑ or NS	Unknown
IL-10	↑	NS or ↑ in convalescent cases	↑
IL-4	↑	NS or ↓ in convalescent cases	NS

Table 1: The levels of cytokines in patients with COVID-19, SARS and MERS versus those in normal controls.

Many cytokines that participate in CSS are not routinely available analytically or are of prohibitive costs for population analysis. However, common biomarkers related to CSS are readily available and inexpensive to test. IL-6, a cytokine prevalent in CSS, is well known to induce the release of C-reactive protein (CRP) [29-31]. IL-6 induces CRP production in the liver by activating Janus kinases. Signal transducers and activators of transcription subsequently switch on the CRP gene expression, leading to the production of CRP [32] state that elevations of serum C-reactive protein and ferritin, which are more readily measured by clinical laboratories than serum cytokines, also correlated with the occurrence and severity of CSS. CRP serves as an adequate and well recognized marker of systemic non-specific inflammation and as a surrogate for IL-6 as they have related roles in the inflammatory response and now as a marker of CSS in COVID-19 [33].

Other non-specific markers of inflammation and endothelial dysfunction are contributing to the diagnosis of a cytokine storm. Erythrocyte sedimentation rate, a non-specific acute phase reactant that is a measure of background inflammation and clotting, is elevated in CSS and COVID-19 [34]. Fibrinogen is a glycoprotein complex that circulates in the blood and, during tissue and vascular injury, it is converted enzymatically by thrombin to fibrin and then to a fibrin-based blood clot. Fibrin clots function primarily to occlude blood vessels to stop bleeding but is also activated to repair non-hemorrhagic damage [35]. People with vascular complications and COVID-19 are reported to have the highest mortality rates. High level of fibrinogen in plasma is recognized as an important vascular risk factor. Fibrinogen level is demonstrated to be a marker of vascular disease, since a parallel effect of cytokines on fibrinogen biosynthesis and on vascular injury was noted by Vasse[36] Acute tissue injury can lead to rapid accumulation of uric acid and urate crystal formation that aggregate in kidneys and induce acute kidney injury [37,38].

Uric acid has been studied in several cardiorespiratory processes that produce hypoxia since this condition leads to increased catabolism of purines. For this reason, uric acid has proven useful as a prognostic marker of heart failure, pulmonary thromboembolism, and primary pulmonary hypertension [39]. Recurrent hypoxia, which is associated with obstructive sleep apnea syndrome (OSAS), leads to an increase in the degradation of adenosine triphosphatase into xanthine, which in turn increases uric acid concentrations. Hypoxia may be a significant feature of COVID-19, although lab data on uric acid values and this disease are not currently available. Loss of heme integrity during SARS-CoV-2 infection through insult on the 1-beta chain of hemoglobin and dissociation of iron from the porphyrin is reported [40]. This event may establish hypoxic tissue conditions that would lead to uric acid upregulation. This data is from an initial report that has not been peer-reviewed. Measuring uric acid values may help corroborate these findings and facilitate patient triage for appropriate late-stage therapy including ventilation or low-pressure oxygen [41]. Disruption of hemoglobin by the virus is reported to trigger the release of iron thus anemia of chronic disease may be driven by SARS-CoV-2. Anemia of chronic disease is immune driven with cytokines and cells of the reticuloendothelial system inducing multiple changes - in iron homeostasis, the proliferation of erythroid progenitor cells, the production of erythropoietin, and the life span of red cells - all of which contribute to the pathogenesis of anemia including elevated serum ferritin levels [42,43]. show a disproportionately high ferritin level in CSS and indicate it may be one of the earlier laboratory findings in disease etiology.

The simultaneous addition of several biomarkers of inflammation in the early diagnosis and risk stratification of CSS, followed by complementary interventions, has the potential to substantially reduce morbidity and mortality from COVID-19. It affords proper patient triaging and may even be useful in determining the best course of treatment including ventilation versus low pressure oxygen and the use of anti-inflammatories to stave off the cytokine storm. However, owing to the relationship between elevated cytokines, represented by acute phase inflammatory markers, and chronic diseases, broad-based

inflammatory markers may find application in early detection of chronic disease, premature aging processes, general morbidity, high medical claims, and early mortality which currently and continually apply stress to our societies [44].

COVID-19 Comorbidity Risk Factors and Impact on non-Lung Tissue

Comorbidities are known to lead to unfavorable COVID-19 outcomes with pre-existing cardiovascular disease showing the highest mortality rates [45-51]. As opposed to the potential miscalculation of death from the virus in the total population due to the long early silent period of the infection, comorbid mortality rates are comparable across diseases and to people with no presumed health conditions. Causality does exist between chronic diseases and severe COVID-19 with chronic patients universally presenting with elevated cytokines. Thus, innate immune activation is an important component in the characterization of these chronic diseases and COVID-19. In addition to systemic and respiratory symptoms, 36% of patients in one study with COVID-19 developed neurological symptoms and the severity of these symptoms was consistent with that of COVID-19 [52]. Neurodegeneration and brain tissue edema were noted in deceased patients [53]. The disease is also noted to cause tissue damage to other organs such as the heart, liver, kidneys, blood and immune system [50,54,55].

According to [56] chlamydia pneumoniae infection is associated with an increased risk of coronary artery disease as is cytomegalovirus, the antibodies of which were found in the Atherosclerosis Risk in Communities Study [57]. Infection and inflammation pre-dispose individuals to higher risk from new infections, a barometer of which includes elevated cytokines and lipoproteins [58]. That azithromycin improves clinical outcomes obtained with hydroxychloroquine in COVID-19 could imply comorbid bacterial infection [59]. Chlamydia and mycoplasma pneumoniae, although not indicated as highly prevalent as a co-infection in COVID-19, based on initial reports, are ubiquitous pathogens. C-pneumoniae pneumonia is often a primary infection in persons aged 7-40 years. Reinfection pneumonia is more common in the elderly. Approximately 50% of young adults and 75% of elderly persons have serologic evidence of a previous infection as indicated by elevated IgG titers [60]. Our evidence, in press, indicates that positive IgG titers are more representative of dormant bacterial infection or those existing in biofilms, not simply a past infection. Thus, the organisms, in this state, are able to reactivate opportunistically. Over 50% of 85 subjects between 19 and 73 years old, employed by a U.S. company and working in the U.S., were positive for chlamydia or mycoplasma pneumoniae IgG antibodies according to our work. When therapeutic protocols for active chlamydia infection were applied to these patients, a wide variety of chronic disease indications and health complaints, including migraines, mood disorders, rheumatoid arthritis, and psoriasis rectified.

Allen postulates that SARS-CoV-2 may create biofilms that, in turn, lead to cytokine production and tissue destruction[61]. Further, it is well documented that more than 90% of microbes live in biofilms and, with pathologic microbes, many disparate diseases seem to be generated by this process [62,63]. These include cutaneous diseases such as atopic dermatitis, psoriasis, leprosy, and many others [64,65]. Internal diseases include arthritis, otitis media, arteriosclerosis, cystic fibrosis, and Alzheimer's disease [66-68]. These reports are consistent with our clinical findings and suggest that total pathogen burden, especially those known to inhabit biofilms, is what dictates high comorbidity mortality in COVID-19.

Measuring Cytokine Storm Biomarkers in Populations

Early into the outbreak of COVID-19, Chinese researchers showed the clinical profile of patients suffering from the disease [69]. They demonstrated that inflammatory markers were elevated, as they are in a cytokine storm, in a substantial number of patients. Among the markers elevated or otherwise out of an optimal range included: procalcitonin; interlukin-6; erythrocyte sedimentation rate; serum ferritin; C-reactive protein; and D-dimer [70].A subsequent study showed elevation in fibrinogen activity [71]. The authors recommended that all patients with severe COVID-19 should be screened for hyperinflammation using laboratory trends based on these markers. Harvard Medical School hospitals subsequently developed a risk stratification protocol for in-hospital COVID-19 sufferers that includes CBC with differential with focus on lymphocyte count, complete metabolic panel, creatine kinase, ferritin, C-reactive protein, fibrinogen, D-dimer, erythrocyte sedimentation rate, markers of tissue deterioration, viral serologies and blood cultures for bacterial infection [72,73]. Levels of cytokines in early COVID-19 patient reports are provided in **Table 2**. Interestingly, many of the values attributable to adverse disease outcomes are "normal" per standard-of-care reference intervals. This represents a significant and continuing problem in the current healthcare delivery model that is designed to determine illness, not pre-illness or predisposition to illness, with few exceptions [74].

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Marker / Study Reference	55	75	24	23	47 Died	47 Lived	70	73	85	Units
Leukocytes	7.5	7		3.9	9.8	5.2		8.2	4.5	X10E3/uL
Neutrophils	5	5.3	4.1	2.8	7.5	4	8.11		3.23	X10E3/uL
Lymphocytes	0.9	0.88	0.86	0.8	0.6	1.1	0.68		0.805	X10E3/uL
NLR	5.56	6.02	4.77	3.50	12.50	3.64	11.93		4.01	
Platelets	214		3.9	105	165	220	147	239		X10E3/uL
Hemoglobin	129		117	131	126	128			120	g/L
D-dimer	900	438	1150	500	5200	600		3075	1105	ng/mL
CRP	51.4	13	32.8	2.5			58	301	21	mg/L
IL-6	7.9		18.3		11	6.3			13.7	pg/mL
ESR	49.9		67						48	mm/hr
Ferritin	808	798	594		1435	503	1006	1216	540	ng/mL
AST	34	46		29					26	IU/L
ALT	39	33	28	24	40	27			26	IU/L
Creatine kinase	85	171			39	18		136		IU/L
Lactate dehydrogenase	336	404			521	253				IU/L
Fibrinogen			510	290					501	mg/dL
Troponin					22.2	3		23		ng/L

Table 2: Potential biomarkers for COVID-19 risk stratification based on initial patient workup.

Three important considerations implore healthcare to consider adopting more robust physiological testing in the general population, including those considered healthy, as part of a routine medical examination.

- PCR and antibody testing may indicate presence or absence of insult but does not provide clinical guidance on how to mitigate current or future manifestations except to affect late-stage emergency interventions, which have low success rates at saving patients[75]. In general, these tests are primarily to design and implement isolation and containment strategies, not affect the survival of infected individuals.
- Pandemics leading to social and economic shutdown have an extraordinary and long-term impact on the stability of society. Population-wide risk stratification may afford more effective, precision- and evidence-based plans on the scope and timing of containment and reopening of society or segments of society.
- The highest reported risks for severe COVID-19 morbidity and mortality are preexisting conditions. We were unable to find evidence-based data that chronic disease management techniques, used in the standard-of-care, are protective against COVID-19. In fact, certain medications are actually indicated to increase risk and severity of the disease. For example, statin drugs, the most widely prescribed of all medications, are reported to increase COVID-19 infection, consistent with acceleration of other infections [76,77]. Immune suppressing drugs have obvious consequences in the face of a disease that challenges nascent immunity [78]. Therefore, the current clinical practices for chronic diseases are minimally effectual at mitigating pandemics.

Here we demonstrate how use of hyperinflammatory markers and other measures of immune health, which are not commonly obtained in the standard of care, are useful in risk stratifying patients for general health, chronic disease risk and, based on the reports cited here, risk for severe COVID-19 outcomes.

Pre-Cytokine Storm Assessment to Mitigate Chronic Diseases – A Population Study

We conducted an open-label, randomized, controlled, before-and-after 6-month study of a high intensity remote and on-site care intervention for mitigation of chronic diseases and risk. Participants included a group of 70 individuals who, at the time, were employed by a mid-west fortune 1000 manufacturing company with approximately 1000 employees at that site. No formal control group was established, however non-participants were tracked using standard metrics of doctor visits and annual medical costs. Participation was voluntary and recruitment started in November of 2016, focused on more chronically sick individuals with higher than average insurance claims, who were motivated to overcome unresolved chronic health issues. Each participant had at least one diagnosed chronic condition, was formerly or currently on a medication for a chronic disease, and was a high healthcare claimant (>$5000/year currently or within the past 3 years) if that data was available. Not all participants had claims data from previous years mainly due to their health plan choice or

employment history with the company. From those interested in the program and met the criteria, retrospective health data (medical claims) were reconciled to finalize the 70-person cohort without consideration for a specific type of condition. Although not a formal clinical study, all procedures performed in the program involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical oversight was provided by the existing primary care clinic management organization, but not under any formal written agreement other than to monitor for patient safety. Informed consent, medical releases, and participation contracts were obtained from all participants included in the program. These documents were completed after each participant was provided detailed information on the program. All data was acquired in strict conformance with health data privacy laws by medical personnel and all stored data were contained on a HIPPA compliant cloud.

The full details of this study are submitted for peer-reviewed publication. The aspects of testing for inflammation and immune status (pre-CSS biomarkers), before and after interventions, are reproduced here, as a model for population risk stratification and COVID-19 risk amelioration. In-clinic vital signs, health risk assessment risk score, and biomarkers were obtained at baseline and at the end of the 6-month program. Problems, complaints and medications were reconciled at each bi-weekly encounter. Fasted and non-fasted blood draws were obtained by clinical PCP staff and were provided to and analyzed by Quest Diagnostics using standard operating procedures. Primary outcomes were changes in biomarker values, risk scores, reported diagnoses, vital signs, weight, and medication use. In over 90% of participants, secondary outcomes demonstrated improvement in reported complaints about energy, pain, sleeplessness, mood, and general wellbeing whereas the control group reported less than 25% subjective health improvement.

The biomarker panel employed is provided in **Table 3**. Many of the markers used to assess and risk-stratify COVID-19 patients were obtained in this study. In addition, we obtained homocysteine, uric acid, and TSH. Further, from these data we determined each participant's neutrophil to lymphocyte ratio (NLR) and atherogenic index of plasma (AIP). In a meta-analysis of six studies of COVID-19, the NLR values were found to increase significantly in patients with COVID-19 severe disease [79,80]. AIP has not specifically been reported as a measure of COVID-19 disease or risk. However, this marker has been reported as superior compared to standard markers at predicting cardiovascular mortality risk in older populations that are at highest risk for COVID-19 mortality [81]. Finally, we developed and evaluated an aggregate risk score, referred to as the chronic disease temperature (CDT). This single score is a combination of 20 physiological biomarker values, **Table 4**. Importantly, the CDT calculation is based on a standardized outcome for all 20 biomarkers, that being an increase in early mortality determined from an exhaustive search in PubMed. Based on this endpoint, we derived a log-linear scale of normal and abnormal values which are substantially different when compared to standard-of-care reference intervals. We assert that the normal and abnormal values used in the CDT calculation more accurately reflect chronic risk and better characterize where an individual resides on the health-disease continuum, whereas the reference interval ranges are designed to established a medical indication requiring a pharmaceutical or surgical intervention. The standard of care reference intervals does not constitute a risk scale, rather it is a yes or no determination of a disease. This type of late-stage disease status measurement does not lend to preventative and non-pharmaceutical amelioration efforts. A current piece of evidence to support this is a report on the increase in cardiovascular mortality among Americans from 2011 to 2016 despite impressive use of cholesterol and blood-pressure controlling medications [82].

Biomarker			
Glucose (fasting)	Protein, Total	LDL Cholesterol Calc	Neutrophils
Hemoglobin A1c	Albumin	C-Reactive Protein	Lymphs
Uric Acid	Globulin, Total	Homocyst(e)ine, Plasma	Monocytes
BUN	A/G Ratio	TSH	Eos
Creatinine	Bilirubin, Total	Insulin (fasting)	Basos
eGFR If NonAfricn Am	Alkaline Phosphatase	WBC	Neutrophils (Absolute)
eGFR If Africn Am	AST (SGOT)	RBC	Lymphs (Absolute)
BUN/Creatinine Ratio	ALT (SGPT)	Hemoglobin	Monocytes(Absolute)
Sodium	Iron, serum	Hematocrit	Eos (Absolute)
Potassium	Vitamin D, 25-Hydroxy	MCV	Baso (Absolute)
Chloride	Cholesterol, Total	MCH	Immature Granulocytes
Carbon Dioxide, Total	Triglycerides	MCHC	Immature Grans (Abs)
Calcium	HDL Cholesterol	RDW	ESR
Magnesium	VLDL Cholesterol Cal	Platelets	Fibrinogen Activity
			Ferritin, Serum

Table 3: Study Biomarker Panel.

Biomarker			
Glucose (fasting)	Atherogenic Index (AIP)	eGFR	Neutrophils %
Hemoglobin A1c	Triglycerides	Homocyst(e)ine, Plasma	NLR
Uric Acid	HDL Cholesterol	WBC	RDW
Insulin (fasting)	LDL Cholesterol Calc	Sed Rate (ESR)	Ferritin, serum
Vitamin D, 25-Hydroxy	C-Reactive Protein	Neutrophils (Absolute)	Fibrinogen Activity

Table 4: 20 Biomarker Panel of the Chronic Disease Temperature Algorithm.

Table 5shows before and after biomarker values and the CDT risk score. The interventions employed to affect the changes in the biomarkers were precision and personalized to each participant and included: lifestyle, diet, supplements and supportive coaching in all instances and pharmaceuticals, when deemed appropriate. The constellation of these interventions may be viewed as a "vaccination" for the innate immune system since a definition of a vaccination is a treatment which makes the body stronger against an infection. As a consequence of the interventions, most participants reduced their overall pharmaceutical usage, **Table 6**.

Biomarker	Mean Before	Mean After	Mean Difference	Standard Deviation	T Test Value	P-Value
CDT	101.32	100.58	0.74	0.79	7.89	<0.0001
A1C	5.67	5.17	0.50	0.45	9.25	<0.0001
Glucose	98.37	95.13	3.24	16.08	1.69	0.0480
NLR	2.17	1.91	0.27	0.92	2.45	0.0083
hs-CRP	2.21	1.77	0.44	1.98	1.86	0.0338
Insulin	9.59	7.06	2.54	5.82	3.65	0.0003
HDL	57.5	61.7	4.23	13.25	2.67	0.0047
Triglycerides	114	101	13	71	1.59	0.0578
Vitamin D	38	60	22	17	10.8	<0.0001
Uric Acid	5.18	5.19	-0.1	0.99	-0.0130	------
WBC	6330	5900	425	1525	2.33	0.0113
RDW	13.8	13.0	0.82	1.00	6.84	<0.0001
Ab Neutrophils	3830	3380	452	1270	2.99	0.0020
ESR	8.49	7.06	1.43	7.58	1.58	0.0598
Fibrinogen	301	295	5.61	61.05	0.77	0.2221
Homocysteine	8.91	9.32	-0.40	2.39	-1.42	------
AIP	0.26	0.20	0.07	0.31	1.84	0.0349
HRA Score	115 (D+)	89 (C)	26	26.30	8.21	<0.0001

Table 5: Before and After Biomarker Values from 6-Month Precision and Personalized Intervention. HRA score is the subjective scoring from a health risk assessment obtained with each lab draw. A letter "grade" is assigned based on score ranges.

Medication	Count	Medication	Count	Medication	Count
Atenolol	2E	Albuterol	1E	Atorvastatin	1E
Spironolactone	1E	Furosemide	1E	Simvastatin	3E
Lisinopril	3E	Topamax	1E	Crestor	2E
Hydrochlorothiazide	2E	Ibuprofen	3E	Enterecept	1A
Omeprazole	6E	Azathioprine	1E	Adalimumab	1A
Lansoprazole	3E	Colace	2E	Naproxen	3R
Prozac	1E	Calcium	3E	Lisinopril	3R
Lexapro	2E	Ferrous Sulfate	1E	Paxil	1R
Zoloft	1E	Alendronate	2E	Simvastatin	5R
Zyrtec	1E	Tamsulosin	1E	Imitrex	1R
Ranitidine	2E	Insulin	1E	Prednisone	1R
Loratadine	2E	Ambien	1E	Naproxen	3R
Flonase	1E				

Table 6: Medication Reduction or Elimination from 6-Month Precision and Personalized Intervention. E=Eliminated; A=Avoided; R=Reduced.

Using biomarkers considered essential in the risk characterization of COVID-19 patients, this study prospectively observed adults with chronic conditions and unresolved health complaints that remained unresolved under usual care treatment. Following 6 months of precision and personalized intervention, participants achieved subjective and objective improvement in health status with 90% seeing a reduction to multiple blood-based biomarkers and 94% achieving a reduction is a broad measure of lifestyle risk factors. Concurrently participants reported weight loss (34% total and 80% of those with a reported weight loss goal), reduction in reported pain, sleeplessness, memory issues, heartburn, skin rashes, migraines, rheumatoid arthritis, and daily fatigue. All those in the program with diabetes had progressively worsened over the previous 2 years, as measured by fasting glucose, HbA1C, and medication usage, improved under this interventional program. We conclude that this overall approach is a model for risk stratification, risk reduction and disease amelioration for the novel coronavirus disease (COVID-19) and chronic diseases broadly.

Management of Late-Stage Cytokine Storms

Treatment of late-stage CSS should be an intervention of last resort. Primarily we must employ measures to illuminate the progression of the disease in individuals before it accelerates, even in the asymptotic phase, causing high mortality regardless of methods employed. The late-stage approach consists of immunosuppression accompanied by attempts to control the underlying triggers of disease. Clearly, antimicrobial agents are warranted for any patient with an infectious trigger, for example in septic shock. Sepsis continues to be a life-threatening syndrome induced by the profound inflammatory response of CSS. As in COVID-19, the most affected organs are the lungs, cardiovascular system, and the kidneys [83-85]. Solutions to late stage disease of any type, including septic shock, seldom yield the results patients desire, with 40% - 60% as the published mortality rate. Yet, according to Gerlach, [86] the inflammatory processes, which play a role in the pathogenesis of diseases like septic shock or other hyper inflammatory states, have certain similarities. Measuring for these similarities in populations will ultimately lead to more impactful solutions. Gerlach further states, "As the mechanisms of cytokine storm are becoming better defined, interventions aiming to interfere with the host response have been undertaken, largely with disappointing results."

With increased understanding of disease mechanisms, targeted therapies for cytokine storm syndromes are becoming more likely but not a current viable solution. Continued focus on fundamental disease mechanisms, coupled with human observational and interventional studies, will allow for more precisely defining populations, including disease phase, in which therapies will be most effective. A precision medicine approach, achieved by properly measuring and understanding the immune mechanisms that lead to CSS in subpopulations, and perhaps even individual patients, is likely to yield benefits in other heterogeneous groups of patients. However, the current choke point is the lack of objective biomarker data, in populations, that are related to causal factors of the disease etiology. Continued basic, translational, and clinical investigation will be needed to make such an approach

possible. This will necessitate capturing inflammatory cytokine information on large populations, and tracking morbidity and mortality statistics that can be analyzed through big data and converted into meaningful interventions.

The characteristics of the cohort and individuals with CSS may yield invaluable data. For example, the results of the original "failed" trial of IL-1β blockade in sepsis were recently reanalyzed to focus only on the subgroup with elevated levels of ferritin [87]. In this subgroup, IL-1β blockade had a beneficial effect that had been lost in the analysis of the entire cohort. The findings in this reanalysis support the need for more robust population evaluation and emphasize that a precision workup differentiating individuals across a broad array of inflammatory and infectious markers will ultimately lead to more optimized immunomodulation interventions.

A precision medicine approach, achieved by understanding the immune mechanisms that lead to cytokine storm in subpopulations, and perhaps even individual patients, is likely to yield benefits in other heterogeneous groups of patients with CSS. Currently, an IL-6 blockade is touted as having "remarkable beneficial effects" [88]. Excessive IL-6 signaling leads to a myriad of biological effects that contribute to organ damage, such as maturing naïve T cells into effector T cells, inducing vascular endothelial growth factor (VEGF) expression in epithelial cells, increasing vessel permeability, and reducing myocardium contractility [89]. The limitations of the current approach, rooted in the complexity and diversity of subjects and the variety of CSS causal factors, may be overcome with better data.

Conclusion

The novel coronavirus has reinvigorated the discussion about vulnerable populations, immunocompromised status, risk stratification, management of chronic conditions, and control of pandemics in a highly connected world. Much effort has been applied to avoidance of this infection, curve flattening, and development of specific treatments with major emphasis on vaccines. However, the identification of cytokine storms in COVID-19 sufferers reminds us that human immunity is complex. Solutions may not lie in preparing adaptive immunity to fight this and future viral pandemics. Consideration of innate immunity and even that of non-specific immunity, may play an important role in protecting populations against acute infectious episodes and even extend to non-communicable diseases that drive up to 90% of morbidity and early mortality impacting the daily quality of life in approximately half of our global population. The concept and definition of "immunocompromised" must be reevaluated and redefined in terms of its accurate, objective measurement and consequential interventions to improve health and not to simply manage disease. The existing model of diagnostics has failed at efficiently and effectively risk stratifying populations. Consequently, policy necessary to balance economic shutdown versus population risk has been universal rather than targeted leading to dramatic and often tragic social and economic consequences. Information from "big data" has contributed little to actionable decisions largely because the preponderance of available objective health data provides little relevance to infectious pandemics. However, this regrettable circumstance also offers the long-term prospective of saving lives if we apply what we are learning about pandemic risk and outcomes to the general measurement of health and disease. The overlap of COVID-19 risk biomarkers and those associated with a myriad of chronic diseases is not coincidence and could be applied to population health today, to risk stratify populations both for chronic disease and pandemic vulnerability. Measuring and acting upon pre-cytokine storm status should be considered for incorporation into the standard of care. The implications of this on policy, human well-being, healthcare resource allocation, interventions, costs, and productivity have the potential to far outweigh the harm created during the COVID-19 outbreak.

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