Physiological Score for the Measurement of Chronic Disease Status and COVID-19 Outcomes

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Keywords: Cytokine Storm; COVID-19; Chronic Disease; Cytokine Rain; Inflammation; Risk Score; Health Score; Preventative Medicine

1. Abstract

The outbreak of disease from SARS-CoV-2, COVID-1, highlights a need for more proactive and predictive models for medical diagnostics and care delivery since immunocompromised individuals are subject to extraordinarily high morbidity and mortality. Those with pre-existing chronic conditions are most likely to present with severe symptoms and die at high rates compared to healthy individuals. However, subjective diagnoses and usual biomarkers do not explain the underlying causal etiologies. Described here is a physiological risk stratification tool, based on cytokine-related biomarkers, that are elevated in sepsis, COVID-19, and also in many chronic diseases. Tools of this nature are necessary to better stratify the future health risk of those with subjective diagnoses or pre-existing conditions and to enhance the characterization of "immunocompromised." It is also an important method to identify the "apparently well" who are without a diagnosis but suffer from insidious chronic disease or have uncovered risks. The information provided by this approach is also likely to explain COVID-19 fatalities in people without pre-existing conditions. Finally, we have coupled this objective risk tool to a detailed, subjective life risk assessment calculator. We report here the results from a cohort of 240 subjects who made changes in subjective measures of health, through health coaching, who showed concomitant changes in objective health, measured through improvement in a multi-biomarker physiological risk score. We also report reversal of serious chronic conditions as a result of this interactive risk mitigation program. We posit that this elegant, yet inexpensive and scalable model of healthcare delivery affords the opportunity to mitigate COVID-19, future pandemics, and chronic diseases by reversing underlying causes of chronic diseases that contribute to adverse health outcomes.

Introduction:

The current pandemic illustrates the vulnerability of our populations to virulent acute infectious diseases. Historically, pandemics have caused major disruptions to normal society. This current pandemic is no exception. And, the outlook for outcomes from future pandemics appear to be no different unless we identify and rectify underlying etiologies associated with infectious pandemic vulnerabilities. The medical community and "big data" have offered little in terms of solutions for individuals. Masks and social distancing offer a false sense of protection. Areas where mask usage was mandated showed a meager 2% reduction in cases [1]. The 2019-2020 influenza vaccine has been 45% effective overall in the United States this season and 55% effective in children, according to preliminary estimates [2]. Pinning hopes on a SARS-CoV-2 vaccine, thus may disappoint. However, healthy people die at approximately 1/12th the rate – at 95% reduction – compared to unhealthy people with diagnosed cardiovascular disease [3].

We have learned that the current standard of care data is not providing adequate information about severe disease causation. For example, measurement of lipids risk based on usual care guidelines is not

useful in predicting COVID risk, as development of hypolipidemia is observed in COVID patients with mild symptoms. The degree of hypolipidemia progressively becomes worse in an association with the disease severity [4]. However, robust testing across the globe is revealing a pattern of pre-existing physiological risk that, when attenuated before, during, or after a pandemic, may reduce its impact on society [5].

Acute Respiratory Distress Syndrome (ARDS) and multiorgan dysfunction are among the leading causes of death in critically ill patients with COVID-19 [6]. Elevated inflammatory cytokines, noted in COVID-19 cases, suggest that cytokine or bradykinin storm syndrome (CSS or BKS), may play a major role in the etiology of COVID-19. Thus, innate immune defenses play a primary defensive role against the virus. Seasonal flu impacts vulnerable populations on both sides of the age spectrum implying that adaptive immunity status is an important aspect of host defense in that disease. However, in COVID-19, that young people are spared suggests that innate immunity is more important in protecting people from adverse symptoms or death in COVID-19 compared to the flu. Further, the flu vaccine was reported by the CDC to be only 45% effective this year, a response level inadequate to mitigate a pandemic. The most vulnerable to mortality from COVID-19, including immunocompromised individuals and those with preexisting disease diagnoses, present with elevated cytokines at baseline. A measure of the innate immune response, and the pre-existing burden of cytokines likely contributes to adverse outcomes [7].

CSS and BKS are not necessarily mutually exclusive. A common denominator is 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 or non-infectious antigen. Susceptibility to COVID-19, in these instances, is subjectively defined as “immunocompromised” status or 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 [8]. The influenza virus is a main cause of those threats and is responsible for millions of severe cases and up to 500,000 deaths each year. 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. 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. These infections, in humans, are accompanied by a raging pro-inflammatory response often without concomitant anti-inflammatory adaptation [4].

~~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. The SARS-CoV-2 may also be creating a systemic hypoxic environment by inhibiting the functioning of Heme [9].~~

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~~COVID-19 attests to the high mutational capacities of coronavirus family members. By extending their reservoir range to include other animal species, 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. 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.~~

In the event of any disease, its severity is the result of the interaction between causal factors and host resistance [10]. This includes essentially all infectious and chronic diseases. A matrix of responses, rather than a single consistent response, is possible. In immunocompromised 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, hyperreactivity 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. In cases like these, poor physiological health was the precipitating feature [11].

There is an urgent need for better risk characterization among populations during and in advance of a pandemic, that accurately identifies the vulnerable. This also means applying better definition to chronic disease etiologies and the concept of “immunocompromised.” This will facilitate enhanced science-based targeted policy decisions compared to the current generalized approach using viral presence (PCR), antibodies, or assumptions about contagion and protection. Co-morbidities and immunocompromised status are clear risk factors for poor COVID-19 outcomes. Clinical management of chronic diseases are not shown to reduce severity and often exacerbates risk as illustrated by high mortality rates in those with pre-existing conditions.

Of certain importance in COVID-19, other pandemics, and chronic diseases is the elevation of common biomarkers, all of which tie back to the innate immune response, CSS, and BKS measurement. Identifying this set of important biomarkers and rectifying causal risk factors leading to their initial elevation, not just managing disease symptoms, offers the opportunity to:

1. Risk stratify those at highest risk for poor outcomes in a pandemic
2. Prepare for pandemics by stratifying populations at risk based on objective measures of physiological health
3. Mitigate pandemics and chronic conditions through proactive measures of risk reversal as opposed to perpetual disease management.

Methods:

We conducted an open-label, randomized, controlled, before-and-after 9-month study of a high intensity remote and on-site care intervention referred to as the Health Revival Program (HRP). The purpose of this study was to demonstrate how modest improvement in health behaviors could improve cytokine storm-related biomarkers and overall chronic health status. Participants included 287 individuals employed by 3 separate companies with each participant covered by their respective health

insurance. Each full participant completed a detailed HRA, obtained a blood panel, and participated in medical and coaching encounters, at least monthly, over the 9-month program. The control was a group of 47 people who agreed to have labs drawn but opted out of the health intervention and risk assessment component of the study. Thus, the study was not blinded. Outcomes in both the study and control groups were measured using our internally developed physiological risk score. Participation was voluntary and those in the study and control groups were required to have at least one pre-existing diagnosed chronic condition or a chronic health complaint that was unresolved.

This was not a formal clinical study, but instead, a low-risk wellness initiative. 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 doctors who were not part of the program. 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 about the program. All data was acquired in strict conformance with health data privacy laws by medical personnel and stored and managed in a HIPAA compliant EMR. All communications with participants occurred within the same system.

Participants in the HRP underwent medical history review, completed a 120 +/- question on-line health risk assessment (Chronic Disease Assessment™ (CDA)) and laboratory testing for 55 serum-based biomarkers (Chronic Disease Temperature™ (CDT)). The control group only acquired the CDT lab panel. The output from the CDA, for the participant, was a letter grade that reflected the subjective measure of their health risk portfolio. The grade is derived from a numeric score obtained by adding the individual risk scores assigned to each question and answer combination in the survey. Health providers obtained a detailed summary of risks and the risk grade from the CDA from which they developed individualized care plans.

HRP participants began one-on-one health coaching encounters upon completing the CDA and CDT. Coaching was based on traditional methods of motivational health coaching and used the output from the CDA as a guide to specific health risks in need of modification. Our doctor, and the non HRP medical doctors, ensured that the recommendations and suggestions made by the health coach did not violate the health coaches license to provide advice. Participants experienced different levels of coaching based on the extent of their risk portfolio and medical needs as determined by the combination of their CDA letter grade and CDT score. Full details of the coaching interventions are provided in a previous publication [12].

Outcome measures focused on the change in physiological health represented by the change in the CDT risk score. The risk score is derived from 21 biomarkers that are useful in characterizing chronic health and risk, most of which are related to the CSS process, Table 1. A detailed explanation of the CDT scoring algorithm is provided in the “Discussion” section. Changes in the CDA risk grade and underlying numeric score were also noted and reported here. In each case, the biomarker panel was obtained prior to the first coaching session and then at approximately the 6-month mark.

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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*	*Sed Rate (ESR)*
Magnesium	VLDL Cholesterol Cal	Platelets	*Fibrinogen Activity*
Ferritin, Serum	*NLR*	*AIP*	

Table 1: Biomarkers obtained in the HRP study. Those in italics are included in the CDT risk score calculation.

Results

Here we demonstrate how broad array of biomarkers, many of which are associated with CSS, BKS, COVID-19, and measures of immune health, not commonly obtained in the standard of care, can be improved through mitigation of life-associated health risks.

Characteristics of the Study Cohort

We collected CDT data from 287 volunteers at 3 separate locations in the mid-West of the U.S. beginning in November or 2016. All of the volunteer participants had at least one chronic disease or condition that was either under active disease management or was considered ill-defined and thus not subject to a standard-of-care intervention. The study spanned an approximate 9-month period for each of the 3 groups, but with different start dates.

Overall, the mean (SD) age of participants in each cohort was 52.6 (16.3) years in the study group and 49.9 (15.6) years in the control with 76% being women in the study group and 69% being women in the control. In the participant group, 93% saw an overall reduction in CDT biomarker score, 4% remained unchanged, and 3% worsened. In the control group 10% of the population improving their score, while 51% were unchanged and 39% worsened. A summary of the before and after biomarker and risk score measurements is provided in Table 2.

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Risk Score	G1 Before	G1 After	G2 Before	G2 After	G3 Before	G3 After	All Before	All After	Ctrl Before	Ctrl After
CDT	101.9	101.0	102.1	100.8	101.5	100.9	101.8	100.9	100.4	100.6
CDA	C- (104)	B- (71)	D+ (115)	C+ (84)	D+ (121)	C (95)	D+ 112	C+ (82)	N/A	N/A
Biomarker										
Insulin	16.0	13.3	10.6	7.1	15.8	11.7	14.3	11.0	15.0	14.2
Glucose	109	98	104	95	114	108	109	100	93	100
A1C	5.8	5.6	5.9	5.2	5.9	5.7	5.8	5.5	5.7	5.7
Triglycerides	123	99	124	101	139	107	128	102	134	127
Uric Acid	5.4	5.0	5.2	5.2	5.6	6.2	5.4	5.4	5.3	5.4
HdL	51	57	58	62	47	50	52	56	56.2	56.6
AIP	0.38	0.24	0.33	0.21	0.47	0.33	0.39	0.26	0.38	0.35
LdL	115	128	118	104	104	99	113	112	129	119
T Chol	190	206	204	192	180	182	191	195	205	204
WBC	6785	6480	6430	5900	6600	5950	6626	6154	6540	6480
Neut Ab	4051	3618	3930	3380	3900	3103	3971	3397	3760	3850
Lymp Ab	2034	2135	1980	1950	2100	2135	2037	2080	1990	1790
NLR	2.0	1.7	2.2	1.9	2.0	1.9	2.1	1.8	1.9	2.2
Neut %	59.7	55.0	64.0	57.0	58.0	52.0	60.5	54.7	55.1	58.1
RDW	13.8	13.4	13.8	13.0	13.7	13.2	13.8	13.2	13.5	13.6
HcY	8.6	9.8	8.9	9.3	11.2	11.3	9.4	10.1	12.0	10.7
hs-CRP	4.1	2.5	2.7	1.8	4.0	2.9	3.7	2.4	2.2	4.1
ESR	6.6	5.1	11.5	7.1	8.3	7.7	8.5	6.5	7.1	10.7
Fibrinogen	323	320	301	285	294	272	308	296	303	315
Vitamin D	32	43	38	60	45	55	38	52	33	38
Ferritin	160	137	102	78	146	80	139	103	166	170
e-GFR nAM	93	95	87	89	80	83	87	91	86	83
e-GRF AM	107	110	94	98	101	105	101	105	104	96
Alkaline P	74	68	64	65	67	65	69	66	76	76
AST	24	22	31	24	29	26	28	24	23	23
ALT	26	22	32	27	32	30	30	26	23	31
TSH	3.2	2.0	3.1	2.6	2.6	2.5	3.0	2.3	2.4	2.6

Table 2: Before and after biomarker and risk score data on 4 groups. Groups G1-3 participated in the HRP intervention. The “All” group is the combined and averaged data from G1-3. The Ctrl group obtained labs at month 1 and month 7 but did not participate in the intervention. The number of participants in each group was: G1, n=99; G2, n=71; G3, n=70; All, n=240; Ctrl, n=47.

Most of the biomarkers used to characterize the populations are consider acute phase reactants, each with different half-lives when elevated by some instantaneous insult [13]. These markers also respond to chronic insults, remaining elevated as long as the insult persists. However, in the case of a chronic insult, the response is subtler. To reduce the impact of acute activation of a given biomarker skewing chronic risk interpretation, the composite CDT score was developed. We consider this score to have much higher chronic risk predictive precision compared to any single marker. Therefore, outcome measurement was based on the CDT before and after values. The CDT is based on a 7-point scale. The change in physiological health, as indicated by % change before and after HRP is provided in Table 3.

Risk Score	G1 % Change	G2 % Change	G3 % Change	All % Change	Ctrl % Change
CDT	27%	37%	21%	28%	-11%
CDA	32%	27%	21%	27%	N/A

Table 3: Relative changes in CDT biomarker risk scores and CDA life risk scores. Groups G1-3 participated in the HRP intervention. The “All” group is the combined and averaged data from G1-3. The Ctrl group

obtained labs at month 1 and month 7 but did not participate in the intervention. The number of participants in each group was: G1, n=99; G2, n=71; G3, n=70; All, n=240; Ctrl, n=47.

This data clearly demonstrates that improvement in the subjective life risk score, the CDA, leads to concomitant improvements in the objective physiological score, the CDT. Reported previously, for study group 2, were remarkable changes in reported and diagnosed health complaints in this population [crossreference]. Thus, we have demonstrated that reducing life risks leads to an improvement in physiological health and a reduction in both medical diagnoses and reported health complaints.

Discussion

The data we present in this study illustrates a lab panel and risk calculator that could be used in standard practice. In essence, the lab panel measures innate immunity while the risk calculator illuminates why the lab values are either optimal or non-optimal. Importantly, the biomarkers, when elevated, are highly correlated to early mortality risk, chronic disease risk, infectious disease risk, and risk of severe COVID-19 outcomes. Each health evaluation tool, the CDA risk assessment grade, and the CDT biomarker panel score, provide a single, simple to understand value that both practitioner and patient may use in outcome and goal setting. In COVID-19, masks and social distancing are the only tools that give some empowerment to individuals. However, we posit that if an individual understands their physiological risk status with respect to poor COVID-19 outcomes, and that status is also tied to actionable life risks, it affords a great level of individual and population empowerment and control over the current confusion and anxiety created by this pandemic.

Chronic Disease Temperature Risk Scale

Paramount to the quality of this study is the measurement tool, the CDT risk score. The chronic disease temperature is a risk score derived from 21 biomarkers, Table 1. Each biomarker comprising the score was exhaustively investigated through literature searches to determine 3 factors used to develop this objective risk predictor.

1. Lab values that show a statistically significant increase in early all-cause mortality or reduction in survival based on more than one peer-reviewed study
2. Hazard ratios for early mortality or reduction in survival for the individual biomarkers
3. Biomarker value ranges used in the development of the hazard ratios

For each marker, we evaluated studies showing the relationship between early all-cause mortality and tertiles, quartiles, quintiles, or deciles of early mortality risk hazard ratios. Regression analysis performed on each data set revealed an approximately log-linear relationship between biomarker value and increase in early mortality risk. Log-linear plots were developed to fit the available data for each biomarker that included an area of “no” or “baseline” risk and escalating, log-linear risk. In some cases, the biomarker exhibited no or baseline risk at a value trending towards zero. In this case, one log-linear curve was developed for the marker. In other instances, for example, white blood cell counts, the “no risk” value constituted a range of non-zero values. In this instance, two curves were produced, on either side of the no risk regime, each with their own hazard ratios and respective log-linear curves. Most of the markers fit into this latter category that describes risk as a “U” curve against biomarker values.

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Finally, each biomarker's risk value data is added together to develop the chronic disease temperature (early mortality) risk score. This algorithm was developed by weighing the contribution of each biomarker towards predicting early mortality through normalizing hazard ratios to a standard and then adding each final risk value to achieve the CDT value. This value is expressed on a scale of 0 to 7, with 7 being obtained when each marker is at the 90th percentile of high risk on their respective log-linear curves. For the purpose of explaining the risk score in medical terms that lay-people can understand, the actual CDT value is added to 98.6 to give the reported "Chronic Disease Temperature" risk value. We determined, through focus groups, that representing the single score on this scale provides more health risk relevance to laypeople compared to using a letter grade or a 0-10 scale value, as possible examples.

Reference intervals used by the major labs to describe "normal" vs "abnormal" biomarker levels, and the CDT biomarker normal values, are often quite different. Reference intervals or ranges are not standardized and can vary from lab-to-lab. In general, normal reference intervals are based on population statistics rather than objective endpoints that remain valid despite changes in society. The ranges of "normal" for the CDT biomarkers usually overlap with the reference intervals but comprise a much narrower range, reflecting a more sensitive signal for chronic disease. This approach is logical when considering the etiology of acute versus chronic conditions. Example reference intervals and CDT normal ranges are provided in Table 4. Trempe et al, provide a detailed explanation of the derivation of CDT biomarker risk assessment [14]. Figure 1 shows example mortality data for biomarkers, the type of which was used in developing the CDT algorithm [15,16].

Add the additional markers – and – after EST and make is 0 - 20

Biomarker	Labcorp Reference Interval 8/2020	CDT Normal Range	Units
Insulin	2.6 - 24.9	2.0 - 6.0	uIU/mL
Glucose	65 - 99	65 - 82	mg/dL
AIP	Not Established	< 0.12	Ratio
T Chol	100 - 199	180 - 250	mg/dL
WBC	3.4 - 10.8	4.0 - 6.0	x10E3/uL
NLR	Not Established	< 1.5	Ratio
Neut %	Not Established	40 - 60	%
RDW	11.6 - 15.4	11 - 12.5	%
HcY	0.0 - 14.5	5.0 - 10	umol/L
hs-CRP	0.0 - 3.0	0.0 - 0.6	mg/L
ESR	0.0- 15	0.0 - 6.0	mm/hr
Fibrinogen Activity	193 - 507	185 - 285	mg/dL
Vitamin D	30 - 100	55 - 85	ng/ml

Table 4: Reference intervals used in the standard of care and normal value ranges based on early mortality data, used in the Chronic Disease Temperature algorithm.

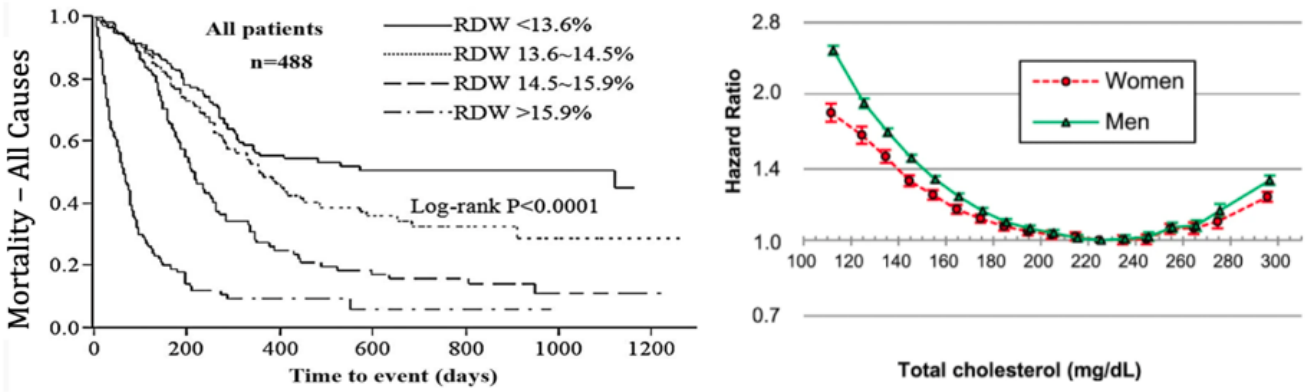

Figure 1: All-cause mortality curves for RDW and total cholesterol. Reprinted by permission. The number of people included in the study for RDW was n=488 and the study for total cholesterol included n=12,800,000.

Cytokines and biomarkers for inflammation in 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. Slightly elevated cytokines are present in cardiovascular diseases. In heart failure, this connection was first reported in 1990 [17]. Subsequently there have been vast publications on elevated inflammatory mediators and acute decompensated heart failure. Mann et al. 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 [18]. 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. In fact, the anti-inflammatory action of statins may be due to the documented antimicrobial action of these drugs, thus their action to mitigate the source of the CSS [19].

Immunotherapy, gaining widespread use across a variety of chronic etiologies, triggers cytokine release. This therapy creates both benefit and harm that is driven by potentially life-threatening compilations of sustained cytokine release [20]. This process, referred to as cytokine release syndrome (CRS), has the potential for fatal complications if the agents leading to CRS are not administered intelligently or are given to people with high pre-existing risk, for example those with already elevated cytokines. In a case-control study on 10 million residents of the Lombardia region of Italy, biologic drug use was shown to significantly increase the risk of COVID-19 hospitalization [21]. Death rates were not increased, but disease severity increased, illustrating the known double-edged aspect of immune suppression approaches. Clearly cytokines must be controlled without compromising immune efficacy.

Overlap between chronic disease and COVID-19 biomarkers

Patients with COVID-19, SARS or MERS present with distinct cytokine profiles, Table 5. In addition, cytokines are considered acute-phase reactants, the half-life of which may interfere with interpretation of chronic risk status depending upon the timing of the disease onset, its severity, and timing of sample acquisition [cross ref to gab]. 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,

chronic disease risk, and poor outcomes in COVID-19, and many late-stage chronic diseases. Evaluating health status, through evaluation of multiple biomarkers, coupled to frequent testing and regression analysis, is an approach seeing more wide acceptance but insignificant implementation [22].

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

Early into the outbreak of COVID-19, Chinese researchers showed the clinical profile of patients suffering from the disease [23]. They demonstrated that inflammatory markers, not just specific cytokines, were elevated in hospitalized 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. A subsequent study showed elevation in fibrinogen activity. The authors in each study recommended that all patients with severe COVID-19 be screened for hyperinflammation. 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 [24]. Levels of traditional and inflammatory biomarkers in COVID-19 patient reports are provided in Table 6. 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.

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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 in China, many of which are used to risk-stratify in-hospital COVID-19 sufferers at Massachusetts General Hospital.
Find Reference

In consideration of the inflammation component of vascular etiologies, cancers, and endocrine disorders and the multi-organ impact of SARS-CoV-2, a role of stealth infection across multiple chronic conditions must not be ignored. A keyword search of PubMed for an association between infection and various chronic diseases shows a remarkable correlation when charted against reports of COVID-19 death rates and preexisting disease, Figure 2A. Interestingly, this search criteria shows a stronger association between infection and heart disease compared to cholesterol and heart disease, Figure 2B. If the association shown in Figure 2A can be shown to have a causal effect as well, then the measurement of pre-cytokine status as it relates to chronic, often stealth, infectious burden, and the resolution thereof, may be an appropriate future path for medical diagnosis and intervention across a broad range of common prolific chronic diseases and SARS-CoV-2 related illness.

Physiological Score for the Measurement of Chronic Disease Status and COVID-19 Outcomes

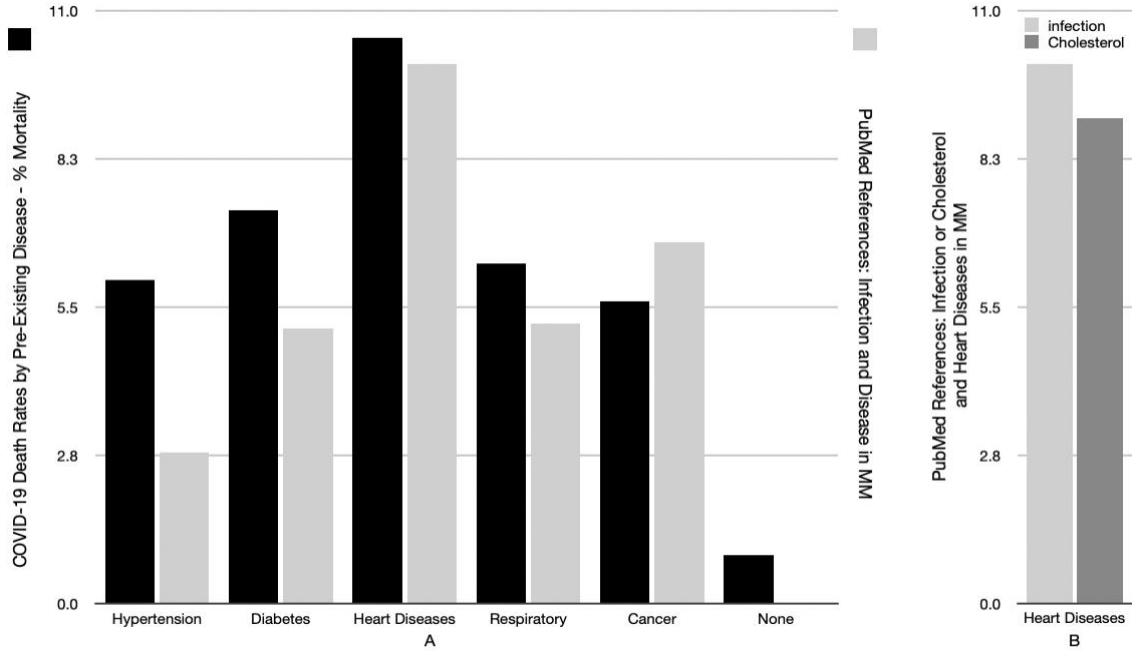

Figure 1A. Mortality rate for COVID-19 with pre-existing disease by percent (black) and number of references in PubMed with an association between the disease and the term "infection" (light gray). Figure 2B. The number of references in PubMed with an association between infection and heart disease (light gray – note this the same data as in Figure 1A for heart disease) and cholesterol and heart disease (medium gray).

Chlamydia pneumoniae infection is associated with an increased risk of coronary artery disease as is cytomegalovirus (CMV) and other pathogens. In the case of CMV, antibodies were found in the Atherosclerosis Risk in Communities Study [25]. Infection and inflammation pre-dispose individuals to higher risk from new infections, a barometer of which includes elevates cytokines and lipoproteins creating CRS [26]. Azithromycin improves clinical outcomes obtained with hydroxychloroquine in COVID-19. This implies comorbid bacterial infection present in these patients and this type of pre-loaded infection is a potential consideration when determining vulnerability. Chlamydia and mycoplasma pneumoniae are ubiquitous pathogens often found in lab testing but seldom associated with chronic disease. C-pneumoniae pneumonia is 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 or current chronic infection as indicated by elevated IgG titers [27].

Our evidence on chronic infection burden in populations, to be published, indicates that positive IgG titers are 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 with concomitant reduction in cytokine and cytokine-related biomarkers (CDT panel) and titers.

Allen postulates that SARS-CoV-2 may create biofilms that, in turn, lead to cytokine production and tissue destruction [28]. Further, he states that more than 90% of microbes live in biofilms and, with pathologic microbes, many disparate diseases appear to be generated by this process, with more research needed to show causal evidence. The diseases include: cutaneous diseases such as atopic dermatitis, psoriasis, leprosy, and many others. Internal diseases include arthritis, otitis media, arteriosclerosis, cystic fibrosis, metabolic disorders, cancer, and Alzheimer's disease [29]. Reports of this nature are consistent with our clinical findings and suggest that total pathogen burdens, especially those known to inhabit biofilms or reside intracellularly, contribute to high comorbidity mortality in COVID-19.

CSS versus a Cytokine Rain biomarkers for chronic disease and COVID-19 risk stratification

When reviewing 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 without strong correlation to the information provided by these tests. Physiological health, the main concern of practicing clinicians, is not articulated through these tests. Further, since the main cause of death from COVID-19 appears to be CSS that is driven more by innate, not adaptive immunity, antibody testing is only a portion of the risk story.

The concept of a cytokine storm is about dramatic acute illness and disease. These mediators, at lower concentrations than in a storm, have essential roles in normal physiology, innate immunity and controlling chronic diseases. A cytokine "rain" that represents the same biomarkers as in CSS, but at levels closer to "normal" is now connected to chronic disease states. According to Clark et al. understanding cytokine storms in their various degrees of acuteness, severity and persistence is essential in order to grasp the pathophysiology of many diseases, and forms a basis for newer therapeutic approaches [30]. This particularly applies to the neurodegenerative diseases according to Clark. In this study, the investigators showed that, 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 COVID-19 severity. Importantly the cytokine "rain" demonstrates predisposition to poor outcomes from COVID-19 and chronic diseases. Since the inflammation stimulated by disease is an immune response and protective against disease, irrespective of collateral damage, cytokine rains (CR) are an expression of a more insidious underlying etiology.

Many cytokines that participate in CSS and CR are not routinely available analytically or are of prohibitive costs for population analysis. However, common biomarkers related to cytokines 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). 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 [31]. Elevations of serum C-reactive protein and ferritin, which are inexpensively measured by clinical laboratories, also correlated with the occurrence and severity of CSS in COVID-19.

Other non-specific markers of inflammation and endothelial dysfunction are contributing to the diagnosis of CSS, CR, and CRS. Erythrocyte sedimentation rate, a non-specific acute phase reactant that is a measure of background inflammation and clotting, is elevated in CSS, many chronic diseases, and COVID-19. 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. 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 across multiple acute and chronic conditions. Fibrinogen in vascular disease has the parallel effect of cytokines impacting fibrinogen biosynthesis and on vascular injury, as was noted by Vasse et al [32].

Acute tissue injury can lead to rapid accumulation of uric acid and urate crystal formation that aggregate in kidneys and induce acute kidney injury. 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. 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 available in the literature. 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 [33]. This event may establish hypoxic tissue conditions that would lead to uric acid upregulation. Measuring uric acid values may help corroborate these findings and facilitate patient triage for appropriate late-stage therapy including ventilation or low-pressure oxygen. 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 explaining the high ferritin levels noted in the disease.

The simultaneous addition of several biomarkers, included those discussed here, in the early diagnosis and risk stratification of CSS, followed by complementary interventions, has the potential to substantially reduce morbidity and mortality regardless of the insult. It affords proper patient triaging and may even be useful in determining the best course of treatment to stave off CSS. 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.

Rationale for measuring and modifying cytokine rains and related markers in standard medical practice

Current health assessments of populations are focused on acute health status and use a very limited set of markers not well suited to determine chronic health and immunocompromised status. Using multiple biomarkers in patient workup improves both precision and accuracy of a diagnosis or risk. COVID-19 is teaching us that physiological health measurement is more important compared to a subjective diagnosis of an indication, like cardiovascular disease, that is assigned based on limited physiological

data. A diagnosis of cardiovascular disease, for example, places all such individuals in the same relative risk category. Whereas, the robust measurement of physiology, and the translation of that measurement into a score, provides a stratification while recognizing that disease status in populations is a continuum. Diabetes assessment provides a reasonable example of risk stratification. People are measured for diabetes risk with both the HbA1C and fasting glucose test. 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, the underlying disease is insulin resistance, yet a fasting insulin test is seldom used. If included it would further enhance placement of a person on the diabetes continuum and should be part of any metabolic disease workup.

Harvard Medical School and other hospitals use a broad set of blood-based biomarkers to risk-stratify in-hospital patients with COVID-19. These same markers, interpreted with consideration of cytokine rain status, applied to populations, may best serve to stratify risk and to set policy on containment strategies in populations. Currently, policy is being established with an incomplete set of evidence and subjective data on individual risk. In vivo blood biomarker analysis offers 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. Importantly, these tests provide an accurate estimate of a person's innate immune and metabolic health, key factors in determining risk in COVID-19 and chronic conditions. Individuals that know and understand their physiological health have more personal control over outcomes when given guidance on how to improve their profile. Both innate and adaptive immunity are important when fighting a virus or other infection. However, innate immunity plays a more important role in chronic disease. Further, innate immunity maintains efficacy against the insult while clever organisms endeavor to evade the adaptive immunity mouse trap.

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 [34]. In general, these tests are primarily used to design and implement isolation and containment strategies, not affect the resilience 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, except in glucose control. 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 published data on acceleration of other infections for people on low total cholesterol. Immune suppressing drugs have obvious consequences in the face of a disease that challenges nascent immunity [35]. Therefore, the current clinical practices for chronic diseases are minimally effective at mitigating pandemics.

Physiological Score for the Measurement of Chronic Disease Status and COVID-19 Outcomes

Treatment of late-stage CSS should be an intervention of last resort. Primarily we must employ measures to illuminate and reverse the disease risk and progression of disease in individuals before it accelerates, even in the asymptotic phase. Solutions to late stage disease of any type, including septic shock, seldom yield the results patients desire, with 40% - 60% being the published mortality rate. According to Gerlach, the inflammatory processes, which play a role in the pathogenesis of diseases like septic shock or other hyper inflammatory states, have certain similarities [36]. 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." This statement confirms the need for early measurement of cytokine rains, then applying interventions to prevent progression to CSS.

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 heterogeneous groups of patients. However, the current choke point is the lack of consistent, standardized use 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, and risk information on large populations while tracking morbidity and mortality statistics that can be analyzed through big data and converted into meaningful interventions. The use of the chronic disease temperature risk score coupled to the chronic disease assessment risk profiling tool may be useful tools in such efforts.

2. 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 and very late-stage interventions. However, the identification of cytokine storms in COVID-19 sufferers reminds us that human immunity against viruses and chronic disease is not just about adaptive immunity. Solutions may not lie in augmenting adaptive immunity with vaccines to fight this and future viral pandemics. Consideration of innate immunity and even that of non-specific immunity like lipid synthesis, 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" and chronic disease status must be reevaluated and redefined in terms of its accurate, objective measurement and consequential interventions to improve health, not simply to manage disease. The existing model of diagnostics and data collection has failed at effectively risk-stratifying populations. Consequently, policy necessary to balance economic shutdown versus population risk has been universal and reactive 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 and chronic disease risk. However, this

regrettable pandemic also offers the long-term prospective of saving lives if we apply what we are learning about susceptibility 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 cytokine rains 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 by the COVID-19 outbreak.

References

1 Liu, Q, Zhou YH, Yang Z (2016) The cytokine storm of severe influenza and development of immunomodulatory therapy. Cellular & molecular immunology 13: 3-10.

2 Clayville LR (2011) Influenza update: a review of currently available vaccines. PT 36:659-684.

3 Taubenberger JK and David MM (2006) 1918 Influenza: the mother of all pandemics. RevistaBiomedica 17: 69-79.

4 Liu Q, Dong-ying L, Zhan-qiu Y (2013) Characteristics of human infection with avian influenza viruses and development of new antiviral agents." ActaPharmacologicaSinica 34: 1257-1269.

5 Wei Z, Wan J, Quain K, Liu X, Xiao Z, et al. (2014) Clinical characteristics of human infection with a novel avian-origin influenza A (H10N8) virus. Chin M J127: 3238-3242.

6 Prompetchara E, ChutitornKetloy C, Palaga T (2020) Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol 38: 1-9.

7 Wenzhong L and Hualan L (2020) (COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. ChemRxiv 2020.

8 Hindson J (2020) COVID-19: faecal–oral transmission?. Nature Reviews Gastroenterology &Hepatology 1-1.

9 Alhazzani W, Moller MH, Arabi YM, Loeb M, et al. (2020) Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive care medicine 28: 1-34.

10 Huang C, Wang Y, Li X, Ren L, Zhao J, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 10223: 497-506.

11 Chen L, Liu HG, Liu W, Liu J, Shang J, et al. (2020) Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Chinese journal of tuberculosis and respiratory diseases 43: E005-E005.

12 Xu Z, Shi L, Wang Z, Zhang J, Huang L, et al. (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine 8: 420-422.

13 van de Veerdonk F, Netea MG, van Deuren M, van der Meer JWM, de Mast Q, et al.(2020) Kinins and Cytokines in COVID-19: A Comprehensive Pathophysiological Approach 4: 43.

14 Lewis TJ (2019) Uncovering Chronic Inflammation and Hidden Infections. Talbott TN. Pp: 85.

15 Liu Q, Yuan-hong Z, Zhan-qiu Y (2016) The cytokine storm of severe influenza and development of immunomodulatory therapy. Cellular &molecular immunology 13: 3-10.

16 Levine B, Mayer KL, Fillit HM, Packer M (1990) Elevated circulating levels of tumor necrosis factor in severe chronic heart failure." New England Journal of Medicine 323: 236-241.

17 Mann DL (2015) Innate immunity and the failing heart: the cytokine hypothesis revisited." Circulation research 116: 1254-1268.

18 Glynn RJ, MacFadyen JG, Ridker PM (2009) Tracking of high-sensitivity C-reactive protein after an initially elevated concentration: the JUPITER Study. Clinical Chemistry 55: 305-312.
19 Lewis TJ (2019) Quarterback Your Own Health: How to Take and Lower Your Chronic Disease Temperature. Talbott TNPp: 125.
20 Gulses A, Matthias G, Açil Y (2013) Cytokine Storm Following Tooth Extraction: An Alternative Hypothesis for Fever and Hypotension in the Immediate Postoperative Period. 12: 313.
21 Surveillances V (2020) The Epidemiological characteristics of an outbreak of 2019 Novel Coronavirus Diseases (COVID-19)-China, 2020. China CDC Weekly 2: 113-122.
22 Wu Z and McGoogan JM (2020) Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 323:1239-1242.
23 Liu Y, Sun W, Guo Y, Chen L, Zhang L, et al. (2020) Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study." Platelets (2020): 1-7.
24 Guo W, Li M, Dong Y, Zhou H, Zhang Z, et al. (2020) Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020: e3319.
25 Gabay C and Kushner I (1999) Acute-phase proteins and other systemic responses to inflammation. New England journal of medicine 340: 448-454.
26 Wang TJ, Gona P, Larson MG, Tofler GH, Levy D,et al. (2006) Multiple biomarkers for the prediction of first major cardiovascular events and death. New England Journal of Medicine 355: 2631-2639.
27 Zethelius B, Berglund L, Sundstrom J, Ingelsson E, Basu S, et al. (2008) Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. New England Journal of Medicine 358: 2107-2116.
28 Liu B, Li M, Zhou Z, Guan X, Xiang Y (2020) Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)induced cytokine release syndrome (CRS)? . J Autoimmun 2020: 102452.
29 Bermudez EA, Rifai N, Buring J, Manson JE, Ridkar PM (2002) Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. Arteriosclerosis, thrombosis, and vascular biology 22: 1668-1673.
30 Rasic I, Rebic V, Rasic A, Aksamija G, Radovic S, et al. (2018) The Association of Simultaneous Increase in Interleukin-6, C Reactive Protein, and Matrix Metalloproteinase-9 Serum Levels with Increasing Stages of Colorectal Cancer. Journal of oncology 2018.
31 Pradhan AD, Manson JE, Rifai N, Buring JE, Ridkar PM (2001) C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. Jama 286: 327-334.
32 Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherain S, et al. (2016) CD19 CAR-T cells of defined $CD4^+$: $CD8^+$ composition in adult B cell ALL patients. The Journal of clinical investigation 126: 2123-2138.
33 Canna SW and Edward MB (2012) Making sense of the cytokine storm: a conceptual framework for understanding, diagnosing, and treating hemophagocytic syndromes. Pediatric Clinics 59: 329-344.
34 Wang F, Nie J, Wang H, Zhao J, Xiong Y, et al. (2020) Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia." The Journal of infectious diseases (2020): jiaa150.
35 Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, et al. (2020) ISTH interim guidance on recognition and management of coagulopathy in COVID-19. Journal of Thrombosis and Haemostasis (2020).
36 Vasse M,Paysant J, Sorai J,Collet JP, Vannier JP, et al. (1996) Regulation of fibrinogen biosynthesis by cytokines, consequences on the vascular risk. Pathophysiology of Haemostasis and Thrombosis 26: 331-339.

37 Wilson FP and Berns JS (2014) Tumor lysis syndrome: new challenges and recent advances. Advances in chronic kidney disease 21: 18-26.
38 Chawla, LS, Amdur RL, Faselis C, Li P, Kimmel PL, et al. (2017) Impact of acute kidney injury in patients hospitalized with pneumonia. Critical care medicine 45: 600-606.
39 Hirotsu C, Tukif S, Guindallini C, Mazzotti DR, Bittencourt LR, et al. (2013) Association between uric acid levels and obstructive sleep apnea syndrome in a large epidemiological sample. PloS one 8: e66891.
40 Ñamendys-Silva SA (2020) Respiratory support for patients with COVID-19 infection. The Lancet Respiratory Medicine 8: e18.
41 Weiss G and Lawrence TG (2005) Anemia of chronic disease. N Engl J Med 352: 1011-1023.
42 Shaw TY and Michael S (2016) Weathering a cytokine storm: a case of EBV-induced hemophagocyticlymphohistiocytosis. J Investig Med High Impact Case Rep 4: 2324709616647409.
43 Pawelec G, Goldeck D, Derhovanessian E (2014) Inflammation, ageing and chronic disease. Current opinion in immunology 29: 23-28.
45 Yang J, Zheng Y, Gou X, Pu K, et al. (2020) Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. International Journal of Infectious Diseases 94: 91-95.
46 Wu Z and McGoogan JM (2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention JAMA.
47 Zhou F, Yu T, Du R, Fan G, Liu Y, et al.(2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 395: 1054-1062.
48 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, et al. (2020) Clinical characteristics of 2019 novel coronavirus infection in China N Engl J Med 382:1708-1720.
49 Huang R, Zhu L, Xue L,Lui L, Yan X, et al. (2020) Clinical findings of patients with coronavirus disease 2019 in Jiangsu Province, China: a retrospective, multi-center study. 2020. SSRN Electronic Journal.
50 Wang D, Hu B, Hu C, Zhu F, Liu X, et al. (2020) Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus–Infected pneumonia in Wuhan, China. JAMA323:1061-1069.
51 Chen T, Wu D, Chen H, Yan W, Yang D, et al. (2020) Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 368:m1091.
52 Jasper Fuk-Woo J, Chang K, Kwan-Yue Choi G, Kai-Wang To K, Tse J, et al. (2013) Differential cell line susceptibility to the emerging novel human betacoronavirus 2c EMC/2012: implications for disease pathogenesis and clinical manifestation. J Infect Dis 207: 1743-1752.
53 Xu Z, Shi L, Wang Y, ZhangJ, Huang L, et al. (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 8: 420-422.
54 Chen N, Zhou M, Dong X, Qu J, Gong F, et al. (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395: 507-513.
55 Vuorio A, Watts GF, Kovanen PT (2020) Familial hypercholesterolemia and COVID-19: triggering of increased sustained cardiovascular risk. Journal of internal medicine (2020).
56 Sorlie PD, Nieto FJ, Adam E, Folsom AR, Shahar E, et al.(2000) A prospective study of cytomegalovirus, herpes simplex virus 1, and coronary heart disease: the atherosclerosis risk in communities (ARIC) study. Archives of internal medicine 160: 2027-2032.
57 FeingoldKR and Grunfeld C (2019) The effect of inflammation and infection on lipids and lipoproteins." Endotext [Internet].

58 Gautret P, Lagier JC,Parola P, Hoang VT, Meddeb L, et al. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label nonrandomized clinical trial. International journal of antimicrobial agents (2020): 105949.

59 Burillo A and Bouza E (2010) Chlamydophilapneumoniae. Infect Dis Clin North Am 24:61-71.

60 Allen HB (2020) Examining Covid 19 from a Novel Perspective.Emerg Infect Dis Diag J 2: 1-5.

61 Tasneem U, Yasin N, Nisa I, Shah F, Rasheed U, et al. (2018) Biofilm producing bacteria: A serious threat to public health in developing countries. J Food SciNutr 1: 25-31.

62 Allen HB (2019) The essential role of biofilms in alzheimers disease. Microbiol Infect Dis 3: 1-3.

63 Allen HB, Vaze ND, Choi C, Hailu T, Tulbert BH, et al. (2014) The presence and impact of biofilm-producing staphylococci in atopic dermatitis. JAMA dermatology 150: 260-265.

64 Carter JD (2006) Tumour necrosis factor inhibition causing psoriasis? A more plausible explanation exists." Ann Rheum Dis 65: 1680-1680.

65 Kalayoglu MV, Peter L, Gerald IB(2002) Chlamydia pneumoniae as an emerging risk factor in cardiovascular disease. Jama 288: 2724-2731.

66 Balin, BJ, Little CS, Hammod CJ, Appelt DM, Gerard HC,et al. (2008) Chlamydophilapneumoniae and the Etiology of late-onset Alzheimer's disease." Journal of Alzheimer's Disease 13: 371-380.

65 Miklossy J (2011) Alzheimer's disease-a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. Journal of neuroinflammation 8: 90.

66 Zhou B, She J, Wang Y, Ma X (2020) Utility of ferritin, procalcitonin, and C-reactive protein in severe patients with 2019 novel coronavirus disease.

67 Mehta P,McAuley DF, Brown M, Sanchez E, Tattersall RS, et al. (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet 395: 1033-1034.

68 https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-considerations-in-children

69 Kox M, Frenzel T, Schouten J, van de Veerdonk F, Pickkers P, et al. (2020) No indications for overt innate immune suppression in critically ill COVID-19 patients.medRxiv (2020).

70 https://www.healthrevivalpartners.com/post/acute-vs-chronic-lab-values

71 Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, et al. (2020) Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized with COVID-19 in the New York City Area. JAMA2020: e206775.

72 Shrestha SK (2020) Statin Drug Therapy May Increase Covid-19 Infection. Nepalese Medical Journal 3: 2020.

73 Ko HHT, Lareu RR, Dix BR, Hughes JD (2017) Statins: Antimicrobial resistance breakers or makers?.PeerJ5:e3952.

78 Akalin E (2020) Covid-19 and Kidney Transplantation. N Engl J Med (2020).

79 Lagunas-Rangel FA (2020) Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol 2020.

80 Zhang B, Zhou X, Zhu C, Feng F, Jia Q, et al. (2020) Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19.medRxiv (2020).

81 Edwards MK, Michael JB, Loprinzi PD (2017) Atherogenic index of plasma and triglyceride/high-density lipoprotein cholesterol ratio predict mortality risk better than individual cholesterol risk factors, among an older adult population. Mayo ClinProc 92: 680-681.

82 Wall HK, Ritchey MD, Gillespie C, Omura JD, Jamal A, et al. (2018) Vital Signs: Prevalence of Key Cardiovascular Disease Risk Factors for Million Hearts 2022 - United States, 2011-2016. MMWR Morb Mortal Wkly Rep 67: 983-991.

83 Karlsson S, Varpula M, Ruokonen E, Pettila V, Parviainen I, et al. (2007) Incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland: The Finnsepsis study. Intensive Care Med 33: 435-443.
84 Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, et al. (2012) Into the eye of the cytokine storm. Microbiol. Mol. Biol. Rev 76: 16-32.
85 Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, et al. (2020) Coronavirus disease 2019 (COVID-19) and cardiovascular disease. Circulation (2020).
86 Gerlach H (2016) Agents to reduce cytokine storm. F1000Research 5: 2909.
87 Behrens EM and Gary AK (2017) Cytokine storm syndrome: Looking toward the precision medicine era. Arthritis & Rheumatology 69: 1135-1143.
88 Tanaka T, Narazaki M, Kishimoto T (2016) Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy 8: 959-970.
89 Liu B, Li M, Zhou Z, Guan X, Xiang Y (2020) Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)induced cytokine release syndrome (CRS)?. J Autoimmun 2020: 102452.

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[1] https://doi.org/10.1377/hlthaff.2020.00818 Lyu, Wei, and George L. Wehby. "Community Use Of Face Masks And COVID-19: Evidence From A Natural Experiment Of State Mandates In The US: Study examines impact on COVID-19 growth rates associated with state government mandates requiring face mask use in public." Health Affairs 39, no. 8 (2020): 1419-1425.

[2] Dawood, F. S., Chung, J. R., Kim, S. S., Zimmerman, R. K., Nowalk, M. P., Jackson, M. L., Jackson, L. A., Monto, A. S., Martin, E. T., Belongia, E. A., McLean, H. Q., Gaglani, M., Dunnigan, K., Foust, A., Sessions, W., DaSilva, J., Le, S., Stark, T., Kondor, R. J., Barnes, J. R., … Flannery, B. (2020). Interim Estimates of 2019-20 Seasonal Influenza Vaccine Effectiveness - United States, February 2020. MMWR. Morbidity and mortality weekly report, 69(7), 177–182. https://doi.org/10.15585/mmwr.mm6907a1

[3] Herrick, Clare. "Syndemics of COVID-19 and “pre-existing conditions”." Somatosphere (2020).

[4] Wei, X., Zeng, W., Su, J., Wan, H., Yu, X., Cao, X., Tan, W., & Wang, H. (2020). Hypolipidemia is associated with the severity of COVID-19. Journal of clinical lipidology, 14(3), 297–304. https://doi.org/10.1016/j.jacl.2020.04.008

[5] Massachusetts General Hospital. (2020). Massachusetts General Hospital COVID-19 Treatment Guidance.

[6] Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., ... & Tai, Y. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine, 8(4), 420-422.

[7] Ragab, D., Salah Eldin, H., Taeimah, M., Khattab, R. and Salem, R., 2020. The COVID-19 cytokine storm; what we know so far. Frontiers in immunology, 11, p.1446.

[8] Liu, Q, Zhou YH, Yang Z (2016) The cytokine storm of severe influenza and development of immunomodulatory therapy. Cellular & molecular immunology 13: 3-10.

[9] Wenzhong L and Hualan L (2020) (COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. ChemRxiv 2020.

[10] Lewis TJ (2019) Uncovering Chronic Inflammation and Hidden Infections. Talbott TN. Pp: 85.

[11] Liu Q, Yuan-hong Z, Zhan-qiu Y (2016) The cytokine storm of severe influenza and development of immunomodulatory therapy. Cellular &molecular immunology 13: 3-10.

[12] Lewis, Thomas J., Jason H. Huang, and Clement Trempe. "Reduction in Chronic Disease Risk and Burden in a 70-Individual Cohort Through Modification of Health Behaviors." Cureus 12, no. 8 (2020).

[13] Gabay C and Kushner I (1999) Acute-phase proteins and other systemic responses to inflammation. New England journal of medicine 340: 448-454.

[14] Trempe CL, Lewis TJ. Quarterback

[15] Yi, Sang-Wook, Jee-Jeon Yi, and Heechoul Ohrr. "Total cholesterol and all-cause mortality by sex and age: a prospective cohort study among 12.8 million adults." Scientific reports 9, no. 1 (2019): 1-10. https://doi.org/10.1038/s41598-018-38461-y

---

[16] Dai, Yuxiang, Hakuoh Konishi, Atsutoshi Takagi, Katsumi Miyauchi, and Hiroyuki Daida. "Red cell distribution width predicts short-and long-term outcomes of acute congestive heart failure more effectively than hemoglobin." Experimental and therapeutic medicine 8, no. 2 (2014): 600-606. https://doi.org/10.3892/etm.2014.1755

[17] Levine B, Mayer KL, Fillit HM, Packer M (1990) Elevated circulating levels of tumor necrosis factor in severe chronic heart failure." New England Journal of Medicine 323: 236-241.

[18] Mann DL (2015) Innate immunity and the failing heart: the cytokine hypothesis revisited." Circulation research 116: 1254-1268.

[19] S. Jerwood, J. Cohen, Unexpected antimicrobial effect of statins, Journal of Antimicrobial Chemotherapy, Volume 61, Issue 2, February 2008, Pages 362–364, https://doi.org/10.1093/jac/dkm496

[20] Gupta KK, Khan MA, Singh SK. Constitutive inflammatory cytokine storm: a major threat to human health. Journal of Interferon & Cytokine Research. 2020 Jan 1;40(1):19-23.

[21] Damiani G, Pacifico A, Bragazzi NL, Malagoli P. Biologics increase the risk of SARS-CoV-2 infection and hospitalization, but not ICU admission and death: real-life data from a large cohort during RED-ZONE declaration. Dermatologic therapy. 2020 May 1:e13475. 10.1111/dth.13475

[22] Wang TJ, Gona P, Larson MG, Tofler GH, Levy D,et al. (2006) Multiple biomarkers for the prediction of first major cardiovascular events and death. New England Journal of Medicine 355: 2631-2639.

[23] https://doi.org/10.1186/s13054-020-02896-5

[24] https://advances.massgeneral.org/research-and-innovation/article.aspx?id=1184

[25] Sorlie PD, Nieto FJ, Adam E, Folsom AR, Shahar E, et al.(2000) A prospective study of cytomegalovirus, herpes simplex virus 1, and coronary heart disease: the atherosclerosis risk in communities (ARIC) study. Archives of internal medicine 160: 2027-2032.

[26] FeingoldKR and Grunfeld C (2019) The effect of inflammation and infection on lipids and lipoproteins." Endotext [Internet].

[27] Burillo A and Bouza E (2010) Chlamydophilapneumoniae. Infect Dis Clin North Am 24:61-71.

[28] Allen HB (2020) Examining Covid 19 from a Novel Perspective.Emerg Infect Dis Diag J 2: 1-5.

[29] Miklossy J (2011) Alzheimer's disease-a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. Journal of neuroinflammation 8: 90.

[30] Clark IA, Vissel B. The meteorology of cytokine storms, and the clinical usefulness of this knowledge. InSeminars in immunopathology 2017 Jul 1 (Vol. 39, No. 5, pp. 505-516). Springer Berlin Heidelberg. 10.1007/s00281-017-0628-y

[31] Pradhan AD, Manson JE, Rifai N, Buring JE, Ridkar PM (2001) C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. Jama 286: 327-334.

[32] Vasse M,Paysant J, Sorai J,Collet JP, Vannier JP, et al. (1996) Regulation of fibrinogen biosynthesis by cytokines, consequences on the vascular risk. Pathophysiology of Haemostasis and Thrombosis 26: 331-339.

[33] Liu W, Li H. COVID-19: attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. Preprint revised on. 2020;10(04).

[34] Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020;323(18):1775–1776. doi:10.1001/jama.2020.4683

[35] Akalin E (2020) Covid-19 and Kidney Transplantation. N Engl J Med (2020).

[36] Gerlach H (2016) Agents to reduce cytokine storm. F1000Research 5: 2909.