Can the Oxidative Stress Index Predict the Severity of COVID-19?

Harold I. Zeliger and Harvey Kahaner

Abstract— Severity of the COVID-19 disease ranges from imperceptible to death with the aged and those with pre-existing conditions being particularly vulnerable to severe symptoms. Other factors have also been shown to influence COVID-19 severity. These include smoking, vaping and exposure to air pollution. These factors have a one thing in common, all raise oxidative stress. The Oxidative Stress Index, derived from a questionnaire and reflective of oxidative stress level, is proposed as a non-invasive way to predict the severity of COVID-19 in those impacted by the Coronavirus.

Index Terms— Corona virus; COVID-19; COVID-19 severity; Oxidative stress; Oxidative stress index.

I. INTRODUCTION

Oxidative stress (OS), a state of imbalance between free radicals and antioxidants in the body, is well known as a direct cause of non-communicative (environmental) disease as well as an indirect cause of bacterial and viral-causing disease via undermining of the immune system (Zeliger, 2016; Rajah & Chow, 2015; Zaki, et al., 2005). The Oxidative Stress Index (OSI), a non-invasive, questionnaire-based index which numerically quantifies OS, has been shown to be an indicator of the environmental disease severity (Zeliger, 2017). It is proposed here that the OSI can be used to predict disease severity of communicative diseases such as COVID-19.

As originally designed the OSI is a 400+ question entity that incorporates all causes of environmental diseases. These include; age, gender, body weight, genetics and epigenetics, prevalent diseases, symptoms regularly experienced, pharmaceuticals used, toxic chemical exposure, radiation exposure, chronic inflammation and lifestyle choices (including, diet, smoking, regular alcohol consumption, recreational drug use and psychological stress).

Recently, the OSI has been reduced to a condensed, eight-parameter questionnaire that can be rapidly completed by a patient or surrogate to yield results that are within ninety percent of those obtained from the original long form questionnaire (Zeliger 2020). As such, the condensed OSI lends itself to use as a survey tool to predict disease severity.

The OSI may also serve to explain why severe symptoms of COVID-19 are being observed in some people aged 20-44 who, based on the presence of pre-existing conditions and age, are expected to be asymptomatic or have only mild symptoms.

II. METHODS

The hypothesis presented here is based upon a literature review of numerous publications on the association between OS and disease, as well as the use of the OSI as a predictor of the likelihood of disease onset and severity.

III. RESULTS AND DISCUSSION

A. Oxidative Stress

Oxidative stress is a state of imbalance of free radicals and antioxidants in the body. The numerous causes of OS include age, gender, body weight, genetics and epigenetics, prevalent diseases, disease symptoms regularly experienced, pharmaceuticals used, toxic chemical exposure, radiation exposure, chronic inflammation and lifestyle choices (including, diet, smoking, alcohol and recreational drug use) and psychological stress (Zeliger, 2016 and the numerous references contained therein).

Chronic OS is associated with the onset of numerous non-communicative diseases, including type 2 diabetes, heart diseases, respiratory diseases, neuro-degenerative diseases, neuro-developmental diseases, immunological disorders and skeletal disorders (Zeliger, 2016).

OS is also associated with the onset and severity of infectious viral, bacterial, fungal and parasite-carried diseases via immune system suppression (Hughes, 1999; Akaike, 2001; Splettstoesser & Schuff-Warner, 2002; Xu, et al., 2015).

It is well established that the onset of chronic disease leads to multi-morbidity. People with non-communicative diseases subsequently have a high incidence of other non-communicative diseases, as well as more frequent and severe bouts with infectious diseases (Zeliger, et al., 2012; Zeliger, 2014; Andresen, et al., 2006). Viral infections have been shown to be co-morbid with Alzheimer's disease (Honjo, et al., 2009). Co-morbidity has also been established between tuberculosis or malaria and type 2 diabetes (Marais, et al., 2013).

OS is associated with lipid peroxidation, protein and DNA damage (Pizzino, et al., 2017). Lipid peroxidation biomarkers that are typically used to measure OS include F2-iso-prostanes, lipid hydroxides and hydroperoxides, aldehydes and ketones. Of these, malondialdehyde (MDA) level in serum is the most commonly used biomarker to determine OS levels. MDA is stable in serum and is readily and accurately analyzed. Elevated MDA levels are associated with all OS raising parameters.

MDA, as well as other biomarkers are point in time measurements only and can vary up and down as much as 19% over a six-day period, depending upon factors such as

diet, exposure to ambient air pollutants, psychological stress and other life-style factors (Nielsen et al., 1997). In addition, MDA measurements require time consuming laboratory analysis that is not universally available. The Oxidative Stress Index (OSI) was developed to overcome these shortcomings.

B. Oxidative Stress Index (OSI)

The OSI is based upon a yes/no questionnaire that a patient or surrogate can complete. The OSI as originally developed contains 400+ items that address all causes of OS enumerated above. The number of positive items checked add up to the OSI and the higher the OSI, the greater the likelihood of disease onset (Zeliger, 2017). Since its original publication, the OSI has been applied to predicting causes of

specific disease, carrying out public health surveys to assess the impact of proximate chemical discharges, health pre-screening and limited medical care area screening (Zeliger 2019).

C. Condensed OSI Form

The OSI in its original format, can be used to show which specific OS raising parameters need to be addressed to reduce the likelihood of disease onset. At 400+ items, however, considerable time is required for its completion and it has been found to be cumbersome for regular use in clinical settings. To overcome this shortcoming, a new eight item version of the OSI that addresses the causes of OS elevation has been developed (Zeliger, 2020). This condensed version is shown in Table I.

TABLE I: OXIDATIVE STRESS INDEX (OSI) CONDENSED FORM*

1. Age	_____			
2. Personal:	female _____	male _____	height _____	weight _____
All diseases and diagnosed conditions at present time				
For cancer, add the stage (1,2,3 or 4) if known				
3. Diseases:	1. _____	2. _____	3. _____	
	4. _____	5. _____	6. _____	
	7. _____	8. _____	9. _____	
Which of these diseases were diagnosed in the last year				
4. Medications:	Number of medications regularly taken _____			
5. Family history:	Number of the above diseases parents had/have			
	Mother _____	Father _____		
6. Education:	Check highest level achieved			
	_____ some high school	_____ high school graduate		
	_____ some college	_____ college graduate		
	_____ graduate school			
7. Residence:	City _____	State _____		
8. Psychological Stress:	Stressed _____	Anxious _____	Depressed _____	

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The eight items in the condensed form are:

1. Age
2. Gender, height and Weight
3. Prevalent Disease
4. Medications Taken
5. Genetics
6. Socioeconomic Status - Education Level
7. Residence
8. Chronic Psychological Stress

As discussed below, these include all major sources of OS elevation and produce OSI values that are within 90 percent of those obtained using the detailed OSI questionnaire.

The OSI condensed form is based upon health impacts of the various parameters as reported in the literature. The scoring assignments for the individual parameters in the condensed form are based upon experience with the detailed OSI form. The point values assigned to each parameter are based upon those obtained via the detailed OSI questionnaire (Zeliger, 2017).

1) Age

Aging is accompanied by an increase in OS, generally starting around age 40 and continuing throughout life (Epel, et al., 2004; Hou, et al., 2015). In the condensed OSI one point is scored for each decade. For one aged 40-49, one OSI point is added to his or her total, 2 points are added for

one aged 50-59, etc. (Zeliger, 2017).

2) Gender, Height and Weight

Being overweight is associated with elevated OS and the onset of numerous diseases. These include, but are not limited to; hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, breathing difficulties, anxiety and depression as well as endometrial, breast, colon, kidney, liver and gallbladder cancers (CDC, 2015). Gender, height and weight information enables one to determine if the person is of normal weight, is heavy or obese (Willett, 2001). The condensed OSI categorizes weight into three categories; normal, overweight and obese. Normal weight is assigned a value of zero. Heavy individuals are assigned a score of 1 and those who are obese are assigned a score of 2.

3) Chronic Prevalent Diseases

The number of prevalent diseases at the time of OSI measurement is a critical indicator of OS. It is well established that all disease increases OS and hence the OSI (Zeliger, 2016; Zeliger 2017). All diseases have symptoms associated with them. These are individually addressed in the detailed OSI. The OSI condensed form does not probe individual symptoms. Rather, it has been found that assigning five points for each prevalent disease adequately

incorporates elevations in OS associated with the prevalent diseases. Respondents are asked to list all diseases with which they have. Multiplying the number of prevalent diseases by five yields the disease number in the condensed OSI.

4) Medications

Essentially all pharmaceutical medications raise OS (Zeliger, 2017) and all have adverse drug reactions associated with them (Zeliger, 2019b). The detailed OSI form addresses these individually. In the condensed form, one OSI point is assigned for each medication taken.

5) Genetics

Genetics is well known to be a factor in most non-communicable diseases with both genetic traits and epigenetic effects raising OS (Cencioni, et al., 2013; Dato, et al., 2013; Jiang, et al., 2013; Guillaumet-Adkins, et al., 2017). Though all non-communicable diseases are more prevalent in those whose ancestors have suffered from those diseases, parental disease is most closely associated with the likelihood of disease onset in an individual (Awdeh, et al., 2006). In the condensed OSI form, respondents are asked to check which of their prevalent diseases were also prevalent in their parents and each genetic link is assigned a value of one OSI point.

6) Socioeconomic Status – Education Level

Socioeconomic status (SES) is well established as an indicator of detrimental lifestyle choices that raise OS (Mielck, et al., 2014). These lifestyle choices include diets high in fats, sugar, salt or processed foods, tobacco, alcohol and recreational drug abuse, radiation exposure and the need to reside or work in a toxic chemical environment (Zeliger, 2016). SES is also associated with an increased likelihood of having undiagnosed diseases (Bein, et al., 2012; Mielck, et al., 2014; Shaw, et al., 2016).

Educational achievement has been shown to be a valid indicator of SES, with lower SES individuals more likely to lead unhealthy, OS raising life styles and to have undiagnosed diseases (Yin, et al., 2017). In the condensed OSI form, 5 education levels are identified and point values assigned for each as follows:

Some high school	5
High school graduate	4
Some college	3
College graduate	2
Graduate degree	1

7) Residence

In the 21st century, 90 percent of the world's people, regardless of SES, are exposed to air pollution (Combes and Franchineau, 2019; World Health Organization, 2018). All air pollutants are toxic, raise OS in a dose response relationship, impact the OSI and are responsible for the onset of numerous diseases including respiratory diseases, cardiovascular diseases, several cancers and Alzheimer's disease (Combes and Franchineau, 2019; Zhou, et al., 2019; Xia, et al., 2019; Kilian J and Kitazawa M, 2018).

Recently, a method to quantify air pollution impact on disease onset, termed the Air Quality Toxicity Index (AQTI) has been reported (Zeliger, 2020). This method, based upon

the dose response relationship between toxic exposure and OS elevation, enables the classification of air quality for individual locations to be calculated and reported as cumulative annual values.

In America, the United States Environmental Protection Agency (EPA) measures air quality in multiple locations on a daily basis and reports the data on-line as the Air Quality Index (AQI) (EPA, 2019). Worldwide, the World Air Quality Project similarly reports air quality data for hundreds of cities. (World Air Quality Index Project, 2019). On an annual basis, these indices identify the number of days in which the air quality in a given locale is classified as either good, moderate, unhealthy for sensitive groups, unhealthy, very unhealthy or hazardous. Hazard numbers ranging from 1 – 6 have been assigned to the six air quality classifications, as follows (Zeliger, 2020a).

Air Quality Classification	Hazard Number
Good	1
Moderate	2
Unhealthy for Sensitive Groups	3
Unhealthy	4
Very Unhealthy	5
Hazardous	6

The air pollution impact on OSI is obtained by multiplying the number of days per year for each of the six EPA classifications at the residence of the responder by the hazard number for that classification and adding the these up to yield the AQTI total as shown in Table II. As also shown in Table II are the OSI air pollution severities (OSI – AP). These are assigned number values from 0-5, and entered into the OSI condensed form.

TABLE II: ANNUAL AIR QUALITY CLASSIFICATION AS SHOWN BY AQTI

AIR QUALITY CLASSIFICATION	AQTI
Good	365-450
Moderate	451-600
Unhealthy for Sensitive Groups	601-750
Unhealthy	751-900
Very Unhealthy	901-1050
Hazardous	1051 or higher

8) Chronic Psychological Stress

Psychological stress, anxiety and depression are associated with most diseases and are more pronounced as illnesses progress (Sahle, et al., 2020). Each of these three conditions raises OS via the release of hormones that elevate OS. Chronic activation of this stress response system results in disease and triggers numerous health problems (Mayo Clinic, 2019).

Respondents are asked to check if they often feel stressed, anxious or depressed. One point is assigned for each positive response.

The relevance of the OSI to predicting disease onset probability as well as for other applications uses has been previously established (Zeliger, 2017, 2019, 2019a, 2019b, 2019c). When the OSI condensed form values are used as presented here an excellent correlation between standard form and condensed form OSI values occurs, with condensed form values showing less than a 10% variation from standard form values.

To sum up, the point values assigned to each of the

parameters contained in the OSI condensed questionnaire are as follows:

Age: 1 for each decade of age starting at age 40.

Personal: 0,1, or 2, depending upon weight status

Diseases: 3 per prevalent chronic disease

Medications: 1 per prescribed or over-the-counter medication regularly taken

Genetics: 1 per each item checked

Education: 1 to 5, depending upon highest education level achieved

Residence: 0 to 5, depending upon air pollution level at residence

Stress: 0 to 3 depending upon chronic psychological status

IV. OSI VALUES AND DISEASE LIKELIHOOD

The following scale of OSI values has been associated with the likelihood of disease onset. It is suggested here that the same scale can be used to predict COVID-19 severity.

0-15	Indicative of good health
16-30	Disease predicted
31-45	Disease probable
45 or greater	Disease imminent

V. COVID-19

The relevance of OS and the OSI in predicting COVID-19 severity is based on the following:

1. COVID-19 disease has been shown to be of greater severity and resulting in increased numbers of deaths in people aged 65 years and older and those with pre-existing conditions that include hypertension, cardiovascular disease, diabetes, air pollution exposure and smoking history (Emami, et al., 2020; Zhang, et al., 2020; Zhou, et al., 2020; Wu, et al., 2020).
2. Pre-existing diseases and smoking all elevate OS and the OSI (Zeliger, 2016; Zeliger, 2019).
3. Viral diseases are more prevalent and more severe in those with lifestyles that include OS raising practices such as smoking, vaping and regular alcohol consumption (Khomich, et al., 2018; Gualano, et al., 2008).
4. Obesity, which also raises OS, is a risk factor for increased viral disease severity (Honce & Schultz-Cherry, 2019).
5. Lifestyles that reduce OS, such as following the Mediterranean diet, have been proposed to protect against COVID-19 severity (Hopkins, 2020).
6. In the United States, young residents of the deep south and mid-south states have been found to be at much higher risk of death from COVID-19 than their similarly aged cohorts in other states. This effect has been attributed to a higher prevalence of heart disease, lung disease, diabetes, obesity and tobacco smoking (Keiser Family Foundation, 2020).

It has been previously shown that lowering oxidative stress via lifestyle changes and appropriate treating of pre-existing conditions can prevent the onset of numerous chronic diseases and reduce the severity of pre-existing ones

(Zeliger, 2016). Use of the OSI has also been shown to be helpful in exploring which of the known contributors to the onset of Alzheimer's disease are more prevalent (Zeliger, 2019a). It is proposed here that a similar approach can potentially be used to ascertain if particular pre-existing conditions are more prevalent in the severity of COVID-19 after its onset or if, indeed, severity is a function of total oxidative stress, as it the case with other viral infections, such as the common cold (Khomich, et al., 2018). OSI screening of current COVID-19 patients can also potentially be used retroactively to associate OSI ranges with degree of disease severity.

The condensed form of the OSI readily lends itself to an electronic app that can be accessed from computers or cell phones and instantly produces a numerical OSI value. Results can be applied on both micro and macro scales.

On a micro scale, using the condensed form of the OSI, individuals can pre-screen themselves to determine if their pre-existing conditions suggest the potential for severe disease and, if so, seek medical screening for the presence of COVID-19, prior to symptom onset. OSI results can be used to indicate life-style choices that can lower OS and thus potentially lower the severity of COVID-19 disease.

On a macro scale, results from OSI screening can potentially be used to predict the number of COVID-19 cases that can be anticipated in a given locale and thus help health care professionals predict the amount of care that will be required and allocate resources appropriately. The knowledge learned from application of the OSI to COVID-19 can also be applied to future epidemics and pandemics.

Though the hypothesis proposed here is yet unproven, there is no risk in applying the OSI to the prediction of COVID-19 severity, for the procedure is not invasive, and only recommends lifestyle changes that cannot harm. Indeed, lowering OS has been shown to prevent the onset of numerous chronic diseases and reduce severity of pre-existing diseases.

VI. CONCLUSIONS

It is proposed here that the non-invasive Oxidative Stress Index can be used to determine the association between oxidative stress level and severity of COVID-19 disease. Once determined, the OSI can potentially predict a particular individual's risk for severity of the disease as well as lifestyle changes that might reduce disease severity. The OSI could also be used to predict the amount of preparation necessary for treatment of COVID-19 and demonstrate vulnerability to disease onset. Potentially, the OSI could potentially be applied future epidemics and pandemics. Lowering OS via lifestyle changes such as eating a healthy diet and ceasing smoking cannot harm but could very well improve a person's overall health.

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