

viXra – Physics of Biology

Type of article	Original research (August 12, 2020) by Dr. John <u>Ting</u> , Dental and Medical Surgery, 729 Albany Creek Road, Albany Creek Q4035, Australia Email: jycting@hotmail.com
Title	Showing role of Angiotensin-converting enzyme 2 in COVID-19 using novel Fic-Fac Ratio

Abstract

Objectives: We utilize a Case Report of severe acute respiratory distress syndrome (ARDS) from pneumonia together with applications from Fic-Fac Ratio to creatively explain COVID-19's drug and vaccine developments, and mitigation measures to combat the resulting pandemic (declared by World Health Organization on March 11, 2020).

Methods: Diagnostic test 'Accuracy' refers to ability of that test to distinguish between patients with disease, and those without. Our novel Fic-Fac Ratio, which is an acronym that stands for Fictitious-Factitious Ratio, is roughly considered as 'Inverse Accuracy' with higher Accuracy corresponding to lower Fic-Fac Ratio and vice versa. Regarded as tertiary spin-off from mathematically proving open problems in Number theory of Riemann hypothesis (and explaining two types of Gram points), Polignac's and Twin prime conjectures; we succinctly outline the derivation of this Ratio.

Results: 2003 Case Report of 43 year-old male presenting with severe ARDS due to Bilateral Early Lobar Pneumonia of uncertain viral etiology resulting in death at a small Australian regional hospital. ACE is an acronym that stands for angiotensin-converting enzyme. The functions of ACE and its counterpart ACE2 are outlined. Physiological and pharmacological implications of ACE2 also acting as entry receptor for the coronavirus causing COVID-19 infection are detailed. Epidemiological principles on modelling COVID-19 pandemic with 'less accurate' SIR model versus 'more accurate' SEIR model are also presented.

Conclusions: Controlling COVID-19 pandemic and developing effective COVID-19 drugs and vaccine(s) can be creatively explained using Fic-Fac Ratio. International collaboration is generally required to defeat COVID-19.

Box 1. Significance of this study.

Since originating from Wuhan, China in December 2019; crucial medical aspects of COVID-19 with its resulting pandemic (officially declared by World Health Organization on March 11, 2020) were quickly ascertained by astute health workers and epidemiologists from many countries dealing with global COVID-19 patients. Our novel Fic-Fac Ratio can be regarded as a simple mathematical tool to usefully model COVID-19 and help clinicians better understand this deadly infection. This Ratio essentially allows us to relate open problems from Number theory when considered as a frontier branch of Mathematics to COVID-19 from Medicine when considered as other science, technology and biology.

COVID-19 is an acronym that stands for Coronavirus Disease 2019 with severity ranging from asymptomatic, mild, moderate, severe to life-threatening with potential to result in residual chronic debilitating symptoms after recovery. It is a multi-organ disease generally affecting

human lungs to the worst degree. To help ease time constraint of busy front-line health workers interested in reading this paper, its content is mindfully composed to succinctly include selected materials on COVID-19 pandemic – officially declared by World Health Organization (WHO) on March 11, 2020. Caused by highly contagious and moderately virulent SARS-CoV-2, this deadly pandemic has resulted in unprecedented negative global impacts from health and economic crisis with numerous deaths and widespread job losses. With many unknown factors, *lockdown stages* imposed and their subsequent easing to control outbreaks are often implemented by health authorities *on the fly*. Similar to most respiratory virus, spread of infection occurs through direct or indirect contact, $> 5 \mu\text{m}$ size droplet spray in short-range transmission, $< 5 \mu\text{m}$ size aerosol in long-range transmission (airborne transmission).

Through our Fic-Fac Ratio which is regarded as *tertiary spin-off* from mathematically proving open problems in Number theory of Riemann hypothesis (and explaining two types of Gram points), Polignac’s and Twin prime conjectures; we relate open problems from Number theory when considered as a frontier branch of Mathematics to COVID-19 from Medicine when considered as other science, technology and biology. Transmitted between animals and people, zoonotic virus SARS-CoV-2 which originated from Wuhan, China in December 2019 causing COVID-19 has clearly been shown not to be a laboratory construct or a purposefully manipulated virus [1]. The aim of publishing this paper is to promote useful knowledge on COVID-19 pandemic in a creative manner with overall goal to help foster global cooperation between all nations on planet Earth to effectively combat this pandemic. It does not contain any compromising or intrusive materials such as sensitive criticisms on national or international policies from selected countries. International cooperation to effectively combat the pandemic is required with China and US playing crucial roles aided by other big and small countries alike such as Russia, Canada, Great Britain, Germany, Australia, New Zealand, Vietnam and Thailand.

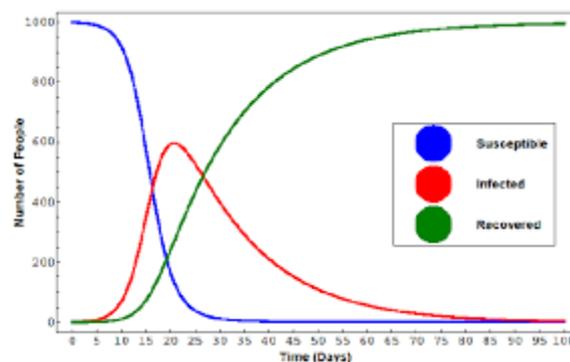


Figure 1. Schematically depicted *SIR* model consisting of three compartments.

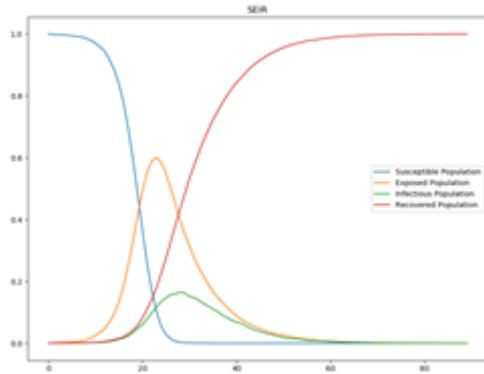


Figure 2. Schematically depicted *SEIR* model consisting of four compartments.

SIR model depicted in Figure 1 and *SEIR* model depicted in Figure 2 are epidemiological (compartmental) models commonly used by mathematicians to compute theoretical number of people inflicted with an infectious illness such as COVID-19 in a closed population over time. Respectively, they consist of three and four compartments derived from: *S* for Susceptible Population, *E* for Exposed Population, *I* for Infectious Population, and *R* for Recovered Population [including deceased and/or immune individuals]. Both models utilize (deterministic) ordinary differential equations – these equations will not be replicated in this paper. Aspects of modelling this pandemic in terms of our derived Fic-Fac Ratio are loosely and intuitively perceived as “Incompletely Predictable” – a term also used when solving the seemingly unconnected above-mentioned open problems in Number theory [2].

The adjective *factitious* derives from *factus* and therefore *facere* means *to correctly make or utilize something based on (true) fact* whereas *fictitious* derives from *fictus* and therefore *fingere* means *to incorrectly make or utilize something based on (false) fiction*. We predominantly refer the “something” here to include mathematical arguments (MA) and diagnostic tests (DT). These two adjectives with their given meanings are used to help create Fic-Fac Ratio, which is an acronym that stands for Fictitious-Factitious Ratio. DT ‘Accuracy’ refers to ability of that test to distinguish between patients with disease, and those without. Roughly considered as ‘*Inverse Accuracy*’ [with higher Accuracy corresponding to lower Fic-Fac Ratio and *vice versa*], we advocate this Ratio to be universally applicable to all well-defined mathematical models.

With or without a “pseudo-component” (respectively) equating to ‘< 100% accuracy’ or ‘100% accuracy’, we usefully categorize all synthesized mathematical models to be broadly associated with either “proposed states” such as Riemann hypothesis or “natural states” such as COVID-19 pandemic. During mathematical modelling of Riemann hypothesis [2], less accurate *inequation* [as opposed to more accurate equation] is the relevant pseudo-component as it contains Pseudo- \sum (all fractional exponents). During epidemiological modelling of COVID-19

pandemic, less accurate “Pseudo-*SIR*” model [as opposed to more accurate *SEIR* model] is the relevant pseudo-component as it does not contain compartment *E* for Exposed Population. Deriving Fic-Fac Ratio is outlined in next section followed by a Case Report of severe pneumonia. By applying this Ratio to open problems, COVID-19 and its resulting pandemic, we subsequently provide concrete examples of ideal gold standard MA and ideal gold standard DT with associated MA and DT results corresponding to Fic-Fac Ratio = 0.

Methods

Abbreviations: MA = mathematical arguments, DT = diagnostic tests, P = Probability (or Proportion), R = Fic-Fac Ratio. We supply definitions, equations and schematic diagram of Fic-Fac Ratio (Figure 3) depicting important inter-relationships for Fic-Fac Ratio which are applicable to MA and DT. Required MA giving [abstract] positive and [abstract] negative MA results in a specified conjecture or hypothesis must be implemented to, respectively, fully **confirm** a “proposed state” to be *correctly valid & correctly not invalid*. Required DT giving positive and negative DT results in a specified subject group or population must be implemented that, respectively, aim to fully **support** a “natural state” to *correctly occur & correctly not occur*.

		Gold standard		for		MA or DT:	
		Positive	Negative	Positive	Negative	Positive	Negative
MA results	or	Positive	Negative	True +ve [a]	False -ve [c]	False +ve [b]	True -ve [d]
	DT results:	Negative	Positive	False -ve [c]	True +ve [a]	True +ve [a]	False -ve [c]

Table 1. The 2x2 contingency table for mathematical arguments (MA) and diagnostic tests (DT).

Based on 2x2 contingency table in Table 1, both MA and DT have parameters forming “stable properties” and “frequency-dependent properties” as depicted below.

Two stable properties:

Sensitivity (Sen) = $a/(a+c)$; Specificity (Spec) = $d/(b+d)$

Four frequency-dependent properties:

Positive predictive value (+ve Pred value) = $a/(a+b)$; Negative predictive value (-ve Pred value) = $d/(c+d)$; Accuracy (Accu) = $(a+d)/(a+b+c+d)$; Prevalence (Prev) = $(a+c)/(a+b+c+d)$

Using Bayes’ theorem, +ve Predictive values can also be calculated as

$$\frac{[(Prev) (Sen)]}{[(Prev) (Sen) + (1 - Prev) (1 - Spec)]}$$

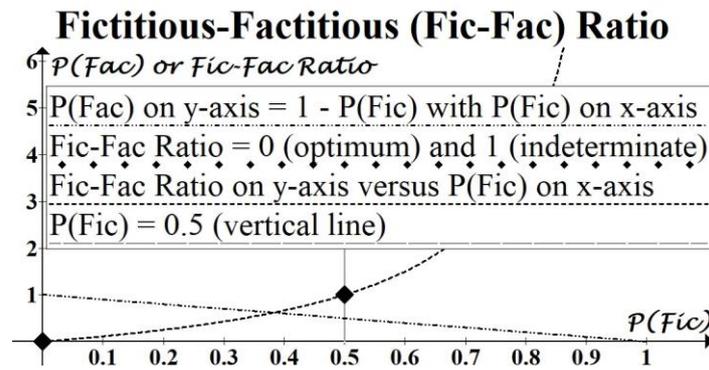


Figure 3. Schematic representation of Fic-Fac Ratio.

Factitious (Fac) = Number of (true) fact = $P(\text{Fac}) = (a+d)$.

Fictitious (Fic) = Number of (false) fiction = $P(\text{Fic}) = (b+c)$.

$P(\text{Fic}) + P(\text{Fac}) = 1 \Rightarrow P(\text{Fac}) = 1 - P(\text{Fic})$... Equation 1

$R = \text{Fic-Fac Ratio} = P(\text{Fic}) / P(\text{Fac})$ with range of values from 0 to ["undefined"] ∞ ... Equation 2

We observe that Fic-Fac Ratio (range: 0 - ∞) is roughly 'Inverse Accuracy' since it varies in opposite direction to that for Accuracy (range: 0 - 1).

Target: Accept $R < 1$ and Reject $R > 1$ with $R = 1$ being indeterminate.

Note: For a well-defined "proposed state" or "natural state", $P(\text{Fic})$ and $P(\text{Fac})$ may each be constituted by ≥ 1 MA or ≥ 1 DT that are mutually independent and/or dependent. Using parameter R (Equation 2), Equation 1 is equivalent to two parametric equations $P(\text{Fic}) = R / (R+1)$ and $P(\text{Fac}) = 1 / (R+1)$ with $(R + 1) \neq 0$ and $R \neq 0$.

Results

Case Report: We outline a Coroner Case of fulminant acute respiratory distress syndrome (ARDS) occurring in a 43 year-old male Caucasian prisoner, AKH, resulting in his death on August 28, 2003 at a small regional hospital in Queensland, Australia. The author was consulted by Emergency Room doctor to take over care of AKH at approximately 01:00 a.m. on that same day whereby he reported 5 to 6 days history of worsening fever, rigors, anorexic, shortness of breath, wheeze, yellow to green sputum, haemoptysis and pleuritic chest pain upon coughing. The history and clinical examination were consistent with severe bilateral pneumonia with initial severe Type 1 Respiratory Failure viz. decreased $\text{PaO}_2 < 60$ mmHg (8.0 kPa) with normal or subnormal $\text{PaCO}_2 < 50$ mmHg (6.7 kPa). Supplementary oxygen therapy and intravenous broad-spectrum empiric antibiotics were prescribed as discussed with on-call respiratory physician. The initial respiratory failure rapidly deteriorated to severe Type 2 Respiratory Failure viz. decreased $\text{PaO}_2 < 60$ mmHg (8.0 kPa) and increased $\text{PaCO}_2 > 50$ mmHg (6.7 kPa) requiring intubation and ventilation at 07:00 a.m. in intensive care unit (ICU). The on-call anaesthesiologist made the decision to transfer AKH to the nearest hospital with larger ICU resources. However, AKH's condition was so unstable that he was unable to be transferred out and he rapidly succumbed to severe respiratory failure with life extinct pronounced about 4¾ hours post-intubation at 11:40

a.m. His death was considered inevitable by the Coroner Court based mainly on autopsy report and subsequent intense scrutiny by another independent respiratory physician.

Plain chest x-ray films from AKH were consistent with ARDS having radiological appearances of bilateral opacities not explained by other lung pathology (e.g. effusion, lobar / lung collapse, or nodules). Clinically, AKH had severe ARDS since his arterial gas analysis fulfilled relevant threshold criteria based on arterial partial pressure of oxygen (PaO₂), fraction of inspired oxygen (FiO₂) and Positive end-expiratory pressure (PEEP) whereby [according to the Berlin definition] severe ARDS is defined as PaO₂/FiO₂ ≤ 100 mmHg with PEEP ≥ 5 cm H₂O. The cause of death was conclusively confirmed on autopsy to be **ARDS** as a consequence of ***Bilateral Early Lobar Pneumonia of uncertain viral etiology***. The coronial inquest delivered on December 22, 2005 was openly published at URL https://www.courts.qld.gov.au/__data/assets/pdf_file/0010/86599/cif-hansen-ak-20051222.pdf by the Coroner Court. It concluded that the maximum cardio-respiratory support provided by the author as Intensive Care medical practitioner and miscellaneous clinical management by other involved health workers were competent. Thus, there was no evidence to suggest that anyone should be committed to stand trial for causing the death.

In *SEIR* model, extra compartment *E* for Exposed Population allows modelling to incorporate *incubation period*. This is time from exposure to causative agent until first symptoms develop and is characteristic for each disease agent. WHO estimated in early 2020 the incubation period for COVID-19 ranges from 1 to 14 days with a median incubation period of 5 to 6 days. One useful way to determine the infectiousness of COVID-19 is the reproductive rate of its causative agent SARS-CoV-2, or R₀. R₀ measures the average number of secondary infections caused by a single case and is initially estimated by WHO to be 1.4 - 2.5 (average 1.95). Higher in countries that do not implement strong public measures such as extensive [and repeated] testing, contact tracing, case isolation and contact quarantine; R₀ is a context specific measurement which will fall to < 1 with successful control of outbreaks. Another [less useful] measure of infectiousness is household secondary attack rate, or the proportion of household members who are likely to get infected from a case. Estimates of this rate have not unexpectedly varied significantly between studies in 2020 [not quoted here], ranging from as low as 3 - 10% to as high as 100% for COVID-19. This suggests factors that vary considerably between different groups such as types of activities, duration of event, ventilation of household and viral shedding of the case. All above estimates can be subsequently refined as more data becomes available.

Four concrete examples utilizing Fic-Fac Ratio (R) are given below whereby their corresponding false positive and false negative MA and DT results do not exist and consequently from Table 1 with (a+d) = 1, (b+c) = 0, and R = 0. For optimal understanding, we discuss [hypothetical] test subject group on MA and patient group on DT with total number of each group

and its two subgroups denoted (respectively) by $N_T = 100$ and $N_1 = N_2 = 50$. Obtaining MA results for a hypothesis or conjecture using ideal gold standard MA to rigorously prove:

(I) Riemann hypothesis [2] to be true via (i) all nontrivial zeros are located on the critical line [true positive MA result] and (ii) all nontrivial zeros are not located away from the critical line [true negative MA result];

(II) Twin prime conjecture [2] to be true via (i) twin primes are infinite in magnitude [true positive MA result] and (ii) twin primes are not finite in magnitude [true negative MA result]; and

(III) Conjecture “Ubiquitous human angiotensin-converting enzyme 2 (ACE2) receptor is sole entry receptor for SARS-CoV-2 causing COVID-19 when susceptible test subjects $N_T = 100$ are [*unethically*] experimentally exposed to this virus with assumed 100% infectivity rate in ideal world (but likely, say, up to around 59% infectivity rate [3] in real world with no implemented public measures)” to be true via (i) COVID-19 infection will occur in test subjects $N_1 = 50$ exposed to SARS-CoV-2 while not taking novel drug ‘*irreversible ACE2 blocker*’ with 100% efficacy and acceptable “safety profile” [true positive MA result] and (ii) COVID-19 infection will not occur in test subjects $N_2 = 50$ exposed to SARS-CoV-2 while taking this same novel drug [true negative MA result].

Obtaining DT results for group of individuals (patient group $N_T = 100$) employing hypothetical ideal gold standard DT with Sensitivity = 100% and Specificity = 100% to definitively determine:

(IV) proportion of patient (i) having [with true positive DT result] COVID-19 infection with $N_1 = 50$ and (ii) not having [with true negative DT result] COVID-19 infection with $N_2 = 50$.

The gene that encodes Transmembrane Serine Protease 2 (TMPRSS2) is activated when male hormones bind to androgen receptor. It can be experimentally shown that TMPRSS2 enzyme [4] is required to cleave SARS-CoV-2’s spike protein – a process known as proteolytic priming – before the virus could enter cells by binding to ACE2 receptor. Pharmacologically targeting (e.g.) ACE2 could theoretically be key to unlocking effective vaccines based on (e.g.) mRNA & DNA nucleic acid, weakened or inactivated viral forms, protein subunits and viral vectors; and effective drugs (e.g.) antiviral medication Remdesivir, ‘androgen deprivation therapy’, ‘irreversible ACE2 blocker’ and ‘TMPRSS2 inhibitor’. Another hypothetical novel drug ‘floating version of ACE2’ could trick the virus to preferably bind with this drug rather than ACE2 on human cells thus potentially treating COVID-19 infection, preventing viral replication and spread.

With main effect of increasing vasoconstricting angiotensin II hormone, ACE acts as a key regulatory peptide in renin-angiotensin-aldosterone system (RAAS); and with main effect of decreasing vasoconstricting angiotensin II hormone, its counterpart ACE2 acts as key counterregulatory peptide via its dual actions of firstly, acting as an ubiquitous functional

receptor present in many parts of our body and secondly, simultaneously acting as an enzyme that predominantly degrade angiotensin II (and to a lesser extent cleaves angiotensin I and participates in hydrolysis of other peptides).

In patients with RAAS blockade such as on ACE inhibitor (ACEI) or angiotensin II receptor blocker (ARB) therapy for hypertension or diabetes, health workers are dealing here with a double-edged sword depending on the phase of disease. Increased baseline ACE2 expression in these patients could potentially increase SARS-CoV-2 infectivity and ACEI / ARB use would be an addressable risk factor. Conversely, once infected, downregulation of ACE2 may be the hallmark of COVID-19 progression. Consequently, upregulation by preferentially employing RAAS blockade and ACE2 replacement in acute respiratory distress syndrome phase may turn out to be beneficial.

“Proposed states” such as modelling Riemann hypothesis when formulated as equation or inequation [with Pseudo- \sum (all fractional exponents)] can and must be error-free. All “proposed states” can and must have their Fic-Fac Ratio = 0 with $P(\text{Fac}) = 1$ and $P(\text{Fic}) = 0$. This is equivalent to stating mathematical-based proofs for “proposed states” must always be mathematically rigorous & error-free.

Loosely speaking, “natural states” such as Pseudo-*SIR* model or *SEIR* model for COVID-19 pandemic are “*Incompletely Predictable*” in the sense that their statistical-based proofs should be statistically significant but they can never be error-free. This is because both models as schematically displayed will (1) intrinsically be affected by obtained DT results using relevant DT e.g. never having, in practice, 100% accuracy and (2) extrinsically be affected by incorrect DT results obtained due to [unintentional] e.g. sampling errors, observational errors, blunders, under- and over-reporting or [intentional] e.g. data fabrication and manipulation. We give an extreme “counter-example” of data fabrication and manipulation: Having ulterior motive, local investigator Mr. CB decided to intentionally send an e-mail containing (say) important test results at (say) 3:45 PM Friday February 8, 2019 to a fabricated email address XYZ. Consequently, these results will never reach the intended recipient (statistician / epidemiologist) for analysis. **Note:** Medico-legally in terms of Fic-Fac Ratio, (i) XYZ is [‘positively’] a *fabricated email address* for recipient when used by Mr. CB since it never belong to recipient = (*abstract*) *True Positive MA* and (ii) XYZ used by Mr. CB is [‘negatively’] a *non-existing email address* for recipient since it was never created by recipient = (*abstract*) *True Negative MA*. This unjustifiable action will lead to failure of these results to be properly incorporated into modelling an “old” epidemic occurring from (say) October 29, 2018 to February 8, 2019. Both (1) and (2) will lead to some quantifiable increase of $P(\text{Fic})$ values [with reciprocal decrease of $P(\text{Fac})$ values] affecting, for instance, I for Infectious Population. Since we generally reject [or accept] probability based Fic-Fac Ratio > 1 [or < 1], the overall goal is to always minimize $P(\text{Fic})$ &/or maximize $P(\text{Fac})$.

Gold standard MA must always be an (error-free) ideal gold standard MA. Gold standard DT refers to its use in achieving a definitive diagnosis obtained by biopsy, surgery, autopsy, long-term follow-up or another acknowledged standard. In theory, an ideal gold standard DT designed to detect SARS-CoV-2 is error-free having Sensitivity = 100% (it identifies all individuals with the disease) and Specificity = 100% (it does not falsely identify individuals without the disease); and consequently will also have +ve Predictive values, -ve Predictive values, and Accuracy all = 100%. In practice, there are no ideal gold standard DT, and one tries to use a DT that is as close as possible to the ideal test. The commonly available reverse transcription-polymerase chain reaction (PCR) test on a nasal (oro/nasopharyngeal) swab detects presence of genetic material of SARS-CoV-2 causing COVID-19. Results on Sensitivity and Specificity of this newly developed test depend critically on how closely it approaches the ideal test. It likely has intrinsic Sensitivity and Specificity in the range of (say) 90 - 95%. Then assuming a high Sensitivity and Specificity of 95% meant that the test could still miss about 5% of infected people and falsely diagnose about 5% of non-infected people.

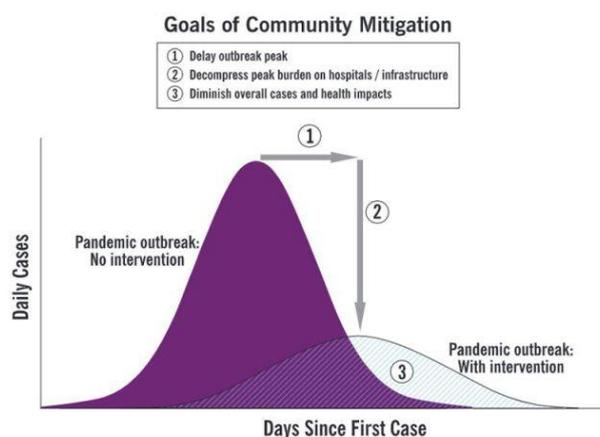


Figure 4. Epidemiological model of pandemic (US Centers for Disease Control and Prevention).

In a study of all 217 passengers and crew on a cruise ship [3], 128 tested positive for COVID-19 on reverse transcription-PCR (59%). Of these infected patients, 19% (24) were symptomatic; 6.2% (8) required medical evacuation; 3.1% (4) were intubated and ventilated; and the mortality was 0.8% (1). The majority of infected patients were asymptomatic (81%, 104 patients). Thus, prevalence of COVID-19 on affected [isolated] cruise ships [and tentatively projected by us to happen in some “hotspot” outbreak places on planet Earth] is likely to be significantly underestimated.

Important Remark: Difference mitigation measures *with full compliance by everyone* could make to severity of COVID-19 pandemic can be clearly illustrated by epidemiological modelling in Figure 4 [*with arising mental health problems being an important addressable issue*]. Dynamic staged implementation and subsequent staged easing of [beneficial] mitigation measures such as *lockdowns, border closures, social distancing* (with practising good hand, cough and sneeze hygiene; obeying more than 1.5 - 2 metres distance between people; using

Personal Protective Equipment (PPE), importantly, in the correct manner when deemed appropriate to do so by authorized health officials for public and health-care settings e.g. eye protection which included visors or face shields or goggles, among others, and three layered homemade cloth face masks or surgical masks or P2 / N95 respirators [5]; and limiting *mass gatherings* are based on experiences, expert opinions, statistical analysis of collected data or previous and recent research studies thus complying with Evidence-based Medicine and Practice.

Ability of a test to discriminate between normal (without disease) and abnormal (with disease) individuals is described by its Specificity and Sensitivity. Generally, they are inversely related to each other and may be altered by changing reference interval or normal range. In other words, one can only be improved at the expense of the other. Example, prostate specific antigen (PSA) cut-off of 4.0 ng/mL [and 3.0 ng/mL] is often given as having a sensitivity of 21% [and 32%] with specificity of 91% [and 85%] for detection of any prostate cancer. A study [6] on conventional Pap smear method to detect cervical cancer in women had Sensitivity 51%, Specificity 66.6%, +ve Predictive value 96%, -ve Predictive value 8% and Accuracy 92%. When a DT has Sensitivity of 95% (5% false -ve) and Specificity of 95% (5% false +ve), for a disease with 1% Prevalence, its +ve Predictive value is only 16% but its -ve Predictive value is 99%. Relationship between Prevalence and +ve Predictive value with Sensitivity of 95% is numerically and graphically depicted in Table 2 and Figure 5.

Disease Prev (%)	+ve Pred value (%)
0	0
0.1	2
1	16
5	50
10	68
20	83
50	95
75	98
99	99.9
100	100

Table 2. Tabulated relationship: Prevalence vs Positive Predictive value with Sensitivity of 95%.

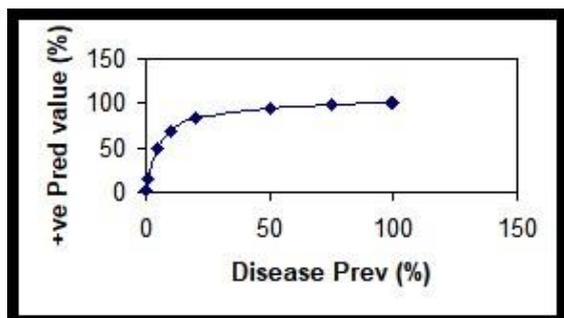


Figure 5. Graphical relationship: Prevalence vs Positive Predictive value with Sensitivity of 95%.

Conclusions

For optimal management of critically ill COVID-19 patients, it is vitally important for world-wide medical communities to share extra knowledge [for instance] that selectively giving nebulized Heparin [7] should reduce severity of COVID-19 induced ARDS through its anti-viral effects, anti-inflammatory effects, anti-coagulant effects, and mucolytic effects; giving corticosteroid Dexamethasone [8] [likely acting non-specifically on various cytokines] through its anti-inflammatory and immunosuppressant effects to appropriate COVID-19 patients with excessive immune response called ‘cytokine storm’ causing harmful hyper-inflammation will reduce the risk of death; and giving Remdesivir which works by inhibiting SARS-CoV-2 viral replication will shorten time to clinical recovery [9].

The original 2002 - 2004 SARS outbreak was an epidemic caused by (comparatively) moderately contagious but highly virulent coronavirus strain SARS-CoV, which is also known as SARS-CoV-1. This outbreak was first identified in Foshan, Guangdong, China on November 16, 2002 spreading to 4 other countries, and subsequently to 29 different countries and territories. Anecdotally, AKH case temporally occurred during the earlier 2002 - 2004 period for this SARS epidemic thus potentially representing a severe and fatal case of SARS-CoV-1 infection. However, this case could also represent the same clinical scenario caused by a severe SARS-CoV-2 infection during the current COVID-19 pandemic in 2020. Due to potentially similar pathophysiological involvement of ACE2 by SARS-CoV-1, SARS-CoV-2, and [perhaps] the unknown virus causing AKH’s severe pneumonia in 2003; we could only speculate whether timely administering nebulized Heparin, intravenous Dexamethasone and Remdesivir to AKH could somehow improve his chance of survival but we suspect not. With retrospective hindsight, we recall that most involved health workers *should have but did not* employ **additional PPE** such as surgical mask and face shields during management of AKH on August 28, 2003. Fortunately, there were no transmission of this presumably minimally contagious viral infection.

The phenomenon and proposed homeostatic mechanism of *supramaximal elevation* in B-type natriuretic peptide and its N-terminal fragment levels in anephric patients with heart failure has been previously outlined in our 2012 paper [10]. Likely also applicable to cytokines, this mechanism consists of analysing the permutations with repetition formula: $n^r = n^2$ from combinatorics involving ‘n’ individual factors that tend to have **non-linear** elevating or lowering properties viz. ‘r’ = 2. We introduce the educational concept of ‘Top-Down Approach’ versus ‘Bottom-Up Approach’ to therapy on COVID-19 induced ‘cytokine storm’ causing hyper-inflammation. We assume the simplistic but not totally accurate caveat expressed through the following statement to be true: *‘Cytokine storm’ is largely caused by imbalance of two broad classes of identifiable cytokines known as pro-inflammatory cytokines and anti-inflammatory cytokines whereby there is supramaximal elevation of the former class with or without*

supramaximal fall of the later class. Then giving Dexamethasone acting through the **non-specific** (increased) anti-inflammatory effect constitutes ‘Top-Down Approach’ to therapy whereby giving novel synthetic drugs ‘Pro-inflammatory cytokine X blocker’ and/or ‘Anti-inflammatory cytokine Y’ acting through, respectively, the **specific** (reduced) pro-inflammatory effect and the **specific** (increased) anti-inflammatory effect will constitute ‘Bottom-Up Approach’ to therapy.

Centers for Disease Control and Prevention (CDC) indicated six stages of vaccine development against a new infection or disease: (i) exploratory, (ii) pre-clinical, (iii) clinical development, (iv) regulatory review and approval, (v) manufacturing and (vi) quality control.

Clinical development is a three-phase process. Phase I: small groups of people receive the trial vaccine. Is the vaccine safe, and what dose should be used? Phase II: clinical study is expanded and vaccine is given to people who have characteristics (such as age and physical health) similar to those for whom vaccine is intended. Can the vaccine generate an immune response? Phase III: vaccine is given to thousands of people and tested for efficacy and safety. Can the new vaccine protect from infection or disease? Many vaccines will also undergo Phase IV formal, ongoing studies after the vaccine is approved and licensed. Through international collaboration, researchers are urgently speeding up the process to obtain globally effective COVID-19 vaccine(s) by running one trial while simultaneously recruiting for next phase.

We have outlined above in Methods an *unethical* thought experiment involving intentionally exposing subject patients to SARS-CoV-2 but we emphasize here that this act is mainly designed to help readers better understand COVID-19. Finally, we opine that only globally available and effective COVID-19 vaccine(s) when successfully developed can ultimately control COVID-19 pandemic. This would be achieved by providing mass immunization targeting sufficient [estimated to be around 60 - 70%] herd immunity threshold [= $1 - (1/R_0)$] at the community level to prevent on-going transmission of this infection.

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