LESSONS LEARNT FROM THE COVID-19 PANDEMIC IN ITALY

Apurva Choudhary[1], Smiline Girija AS[2]

[1]*Saveetha Dental College, Saveetha Institute of Medical and Technical Science, Saveetha University, Chennai.*

[2]*Associate professor, Department of Microbiology, Saveetha Dental College, Saveetha Institute of Medical and Technical Science, Saveetha University, Chennai-600077*

[1]*151801029.sdc@saveetha.com*
[2]*smilinegirija.sdc@saveetha.com*

ABSTRACT

The spread of coronavirus disease 2019 (COVID 19) reached pandemic world-wide especially in Italy from early March 2020. Many factors were under discussion among public health experts for the exorbitant mortality rate in Italy than other countries. A coordinated global response was desperately needed to prepare health systems to meet this unprecedented challenge in Italy. This review illustrates predictions, chronic comorbidities, effects of COVID 19 on Italian health system. Covid disease affecting the elderly population with co-morbidities, the same was associated in the mortality rate among elder population in Italy in a greater rate. The mortality rate in Italy was also higher due to the asymptomatic cases not being tested and isolated with initial screening. The most serious outcome of COVID 19 pneumonia was recorded among the population in Italy. Exhausted number of ICU's beds, ventilators and respirators revealed their un-preparedness for the covid-19 pandemic. This review thus focuses on the various factors to be considered in future pandemics by analyzing the covid - 19 pandemic in Italy.

KEYWORDS: COVID 19, mortality rate, demographic, socio-economic profile, Italy-CoV

INTRODUCTION

The spread of coronavirus disease 2019 (COVID 19) was becoming unstoppable and reached pandemic, having infected more than 100,000 people in 100 countries (Pasquariello and Stranges n.d.). Italy had 226,699 cases with 32,169 deaths and 129,401 recovery until the end of April. Moreover the number of people who recovered or were discharged from hospital after contacting the virus reached 93,000, while the number of deceased reached 30,000. Cluster of pneumonia cases emerged from the city of Wuhan, China and rose as a pandemic wave currently ravaging several countries. The pathogen causing the acute pneumonia among affected individuals is the new coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Wang, Tang, and Wei 2020). Coronaviruses are enveloped non- segmented positive RNA viruses belonging to the family coronaviridae and the order Nidovirales and broadly distributed in humans and other mammals. As of March 12th 2020, laboratories in Italy had diagnosed more than 27,000 people affected by this virus, with 1,016 deaths as shown in Figure 1. A coordinated health response was thus desperately needed to prepare health systems to meet this unprecedented challenge.

Many infected patients were asymptomatic and it was difficult to stimulate the mortality rate (Sterpetti 2020). Italy had the highest pre-value of the disease, with mortality rates higher than in China and South Korea, probably related to the advanced mean age of the Italian population. In particular, Italy had tested more than 5,80,000 people for covid-19 as of April 2, 2020 (Francini et al. 2018). On 8 march 2020, Italian government expanded the quarantine to all of Lombardy and 14 other Provinces, by placing more than 60 million people in quarantine (Sjödin et al. 2020). By 19 May, Italy has tested about 2,000,000

people. But due to the limited number of tests performed, other countries were higher than the official count. On 19 March, Italy became the country with the highest number of confirmed coronavirus deaths; however, In April it was overtaken by the United States (Leung 2020). Covid 19 can be gender biased and has shown more cases among males in comparison to females (Khaerunnisa et al. n.d.) (Mobaraki and Ahmadzadeh 2019). This review thus highlights on various factors that had led to the exorbitant mortality rate in the recent covid-19 pandemic in Italy.

Mortality rate in Italy: An overview

On May 18th, Italy had 2,26,699 cases with 32,169 deaths and 1,29,401 recovery as shown in Figure1. Italy had the highest Covid-19 mortality rate worldwide. Cause for the high mortality rate may be that Italy has a higher number of infected individuals with higher mortality rates. One of the studies showed that the transmission rate from unreported infections was 55% of the rate of reported infections, and 75% from the un-reported cases (Li et al. 2020). Several health care professionals were also the convicts of covid pandemic in Italy. The percentage of people between the age of 30 and 49 years who live with parents is upto 20%, and is considered to be much higher than other european countries. Adults and children, which are often asymptomatic, could have led to the infection to the elderly parents (Iosa, Paolucci, and Morone 2020). Another factor for the highest mortality rate in Italy was due to the asymptomatic cases not being tested and isolated. One of the studies documented that the recognition of asymptomatic patients or cases might have decreased the transmission rates (Callaway 2020). Covid -19 pneumonia was also higher among the males and the fact of high mortality among men was associated with the habit of smoking that had led to respiratory collapse. Many studies had also demonstrated the high global rates of morbidity (4,618,821 infected cases), a sizeable number of individuals have already succumbed (311,847 deaths) (case fatality rate of 1–10%) to severe pathological manifestations involving the lower respiratory tract in Italy (Ruan et al. 2020).

Prediction models associated with increased mortality rate:

Amidst many infection associated models, mathematical predictions provided an indication of the approximate period when a substantial reduction of positive cases and mortalities is expected and not the end of the extremely important mitigation measures (Ciufolini and Paolozzi 2020). Monte Carlo simulations are designed to take the measurement error in each daliy number of cumulative positive cases of COVID 19 in Italy (Rohlf, James Rohlf, and Swofford 1989). Basically this error describes the uncertainty in the process of measuring the daily number of positive cases due to fluctuations in the measurement procedures such as different numbers of performed daily nasopharyngeal swabs of one day with respect to another day (Frisan 2020).

One study demonstrated the mortality rate using a Patient Information Based Algorithm (PIBA). The PIBA uses patient data in real-time to build a model that estimates and predicts death rates for the near future. PIBA uses data of patients identified early in the disease process to calculate the average number of days from hospitalization to death for those hospitalized in Italy. Another feature is to take into account variations based on mathematical models. But most of the models failed to associate various factors involved with the covid - 19 illness in Italy population. Predicted models also suggested the preventive measures such as social distancing, hand hygiene etch., should be strictly followed among the population (Montacer n.d.). Models also showed the development of severe COVID-19 differs among males and females (Ye, Wang, and Mao 2020).

Comorbidities associated with the mortality among n-CoV cases in Italy:

The new coronavirus was harmful to people with pre-existing chronic conditions, which was highly prevalent in the general population especially among the elders (Onder, Rezza, and Brusaferro 2020). Chronic diseases such as hypertension, type 2 diabetes, cancer, chronic kidney disease, stroke, cardiovascular disease (Paramasivam, Priyadharsini, and Raghu Nandhakumar 2020) these are common comorbidities that can be fatal to the coronavirus patients (Lippi et al. 2020). More specifically, a person having a background of respiratory disease was at high risk (Iwasaki and Grubaugh 2020). Italy's elderly population displayed these conditions at a much greater rate. People having respiratory disease or other chronic disease such as cancer showed high chances of infection leading to increased mortality rate in Italy (Backer, Klinkenberg, and Wallinga 2020).

It had also been reported that individuals admitted into intensive care units have significantly elevated levels of IL-6, IL-10, and TNF-α and fewer T cells in circulation and their association with an increased viral load, exacerbated lung injury, and a fatal prognosis (Moon 2020). The median time from development of symptomatic disease to death from CoViD-19 is ~2–8 weeks (Tseng et al. 2005). The onset of cytokine storm in the lungs likely occurs prior to the recruitment of inflammatory cells, especially in allergic patients and those with other comorbidities, leading to an exorbitant rise in mortality rates (Rincon and Irvin 2012). Onset of acute respiratory distress syndrome can be fatal characterized by pneumonitis, pyrexia, myalgia, dyspnoea, loss of smell/taste and can lead to high mortality rates with cytokine storms (Girija et al. 2020a). SARS-CoV-2 appears to trigger a prolonged phase of hypercytokinemia (also called as macrophage activation syndrome) that encompasses a broad array of pro-inflammatory mediators like IL-6, IL-1β, TNF-α, and CXCL8 (IL-8) together with the infiltration of inflammatory and degranulating cells into the lungs, usually 7–10 days following the onset of symptoms during the second stage of CoViD-19 (Tisoncik et al. 2012). The World Health Organization has documented these symptoms are less severe when compared to influenza (Mehta et al. 2020). It occurs when leukocytes become activated leading to an abrupt release of TNF-α, IL-6, IL-1β, and IL-10, which at times can be life-threatening due to the acute onset of hypotensive shock and multi-organ failure (Tanaka, Narazaki, and Kishimoto 2016). Reports on deceased cases with the coronavirus (COVID-19) infection revealed that the majority of cases showed one or more comorbidities and hypertension was the most common pre-existing health condition, detected in 68 percent of patients who died after contracting the virus. Type 2-diabetes, chronic renal failure, and ischemic heart disease were also among the most common comorbidities in COVID-19 patients who lost their lives. The appearance of the closely related TGEV variant porcine respiratory coronavirus (PRCoV) has been found beneficial in preventing TGEV infections, possibly through induction of neutralizing antibodies that can provide cross-protection against TGEV infection

Impact on the Italian health system

One of the most stressful aspects for the Italian National Health System was to provide more intensive care units (ICUs) in local and regional hospitals in Italy for patients with severe acute respiratory syndromes induced by COVID 19. This had nearly exhausted the availability of ICU beds, also respirators and ventilators (Rosenbaum 2020). This situation was most worrisome amidst the cases as they are having fear of not getting the best care from the hospital. According to one study, in the early stage of epidemic, a few small medical facilities, perhaps overwhelmed by the number of symptomatic hospitalized patients and severity of their conditions, may have failed to follow safety procedures and so furthered the spread of the virus among other patients with serious illness as well as to visitors and medical personnel (Michelozzi et al. 2020). Previous study demonstrated a cohort of 41 laboratory-confirmed CoViD-19 patients in Wuhan, China, subjected to serological evaluation, revealed high levels of IL-1β, IFN-γ, IP-10, and MCP-1, of all the 22 cytokines tested among both ICU as well as non-ICU cases. It has also become evident that

in moribund cases, cytokine storms were highly associated with the magnitude of disease severity (Wu et al. 2020). A recently published CoViD-19 research has shown encouraging results with no evidence of any serious adverse events (Shimabukuro-Vornhagen et al. 2018). Multicenter randomized-controlled trial of tocilizumab had been approved for CoViD-19 pneumonia (ChiCTR2000029765) (Chapman and Webster 2013). Though many vaccines showed cross-protection, hepatitis B vaccination is not effective for CoViD-19 (Pratha, Ashwatha Pratha, and Geetha 2017). Co-Occurrence of drug resistant bacteria like Acinetobacter baumannii is quite common with various viral disease, these sort of co-infections were left out of check (Girija As and Priyadharshini J 2019)(Girija, Jayaseelan, and Arumugam 2018). In most of the co-infection, severity is more due to the plasmid and genome encoded resistance too (Girija As and Priyadharshini J 2019, Smiline, Vijayashree, and Paramasivam 2018). The herd immunity and the immunity levels were also considered to be too low in the Italian community, as we are aware the innate immune mechanisms may vary based on the genetic maik-up of an individual (Paramasivam, Priyadharsini, and Raghunandhakumar 2020, Priyadarshini et al. 2018a) (Priyadarshini et al. 2018b).

Socio-economic Condition

Italy is a western democratic country where restrictions to daily liberties are difficult to enforce in a draconian fashion. Due to the lockdown of the entire country, the economy was decreasing. The diffusion of the internet and related technologies was low among the elderly, the most at-risk category (Buja et al. n.d.). Due to the long term lockdown, a high reduction in the economic status with additional negative impact on the well being of the most vulnerable population subgroups could be expected. One of the studies shows that the financial impact is a big concern for banks across Asia and Europe, in the corporate segment, there are obvious pressure points, such as the travel and airlines industries. But there are likely to be repercussions across the economy, as demand for goods and services have massively reduced in Italy (Bari et al. n.d.). This also had a major impact in the recent covid pandemic in Italy

Preventive strategies implemented in Italian covid pandemic:

Deaths in Italy were going higher in other equally affected countries due to its unique demographics and socioeconomic profile. In addition we cannot ignore the stress on the health care system imposed by COVID 19 sudden pandemic in the most affected areas of the country, in terms of death troll. There was a need to increase ICU beds and create new hospitals in all the countries. It was difficult to determine the percentage of contaminated patients, symptomatic or not, and who will require intensive care. Ventilatory assistance was required in about 10% of hospitalized patients as the mortality rate was increasing in the respiratory disease patients. Availability of additional beds was recovered from private clinics (Koh 2020). In this period, the possibility of a diffuse contamination of the hospital workers being highly probable an emergency room can be best prepared and set earlier. Government seeked help from other countries for masks and mechanical ventilators (Grasselli, Pesenti, and Cecconi 2020). This could have also helped in the decrease in mortality rate and control of infection. Various drugs were used including antivirals, antimalarials and also tocilizumab in patients with high levels of interleukin 6 and extensive bilateral pulmonary lesions (Anderson et al. 2020). Tocilizumab (a recombinant humanized anti-human IL-6 receptor monoclonal antibody) specifically binds sIL-6R and mIL-6R to inhibit signal transduction and has been well-tolerated as established in animal drug trials (Kaly and Rosner 2012). Chlorhexidine is not effective in coronavirus as depicted in one study (Selvakumar and Np 2017)(Shahana and Muralidharan 2016).

Putative vaccine peptide design (Girija et al. 2020b)(Girija et al. 2019), currently implemented for various diseases, can be applied to design novel vaccines against covid too. The appearance of the closely related TGEV variant porcine respiratory coronavirus (PRCoV) has been found beneficial in cross protections (Marickar, Geetha, and Neelakantan 2014). Antibacterial activities based on natural herbs can be a

preventive measure for coronavirus (Vaishali and Geetha 2018) (Ashwin and Muralidharan 2015). Anti inflammatory action can inhibit the spread (M, Geetha, and Thangavelu 2019). Countries in Europe, like Italy, Spain, the United Kingdom, and the United States delayed implementing containment measures and failed in anticipating the impact of the pandemic in their own boundaries. An exceptionally high degree of understanding was lacking among the Italian population and acceptance of these measures was also critical. The intervention had an imbalance too with getting back to normal life and everyday activities to the best extent possible and reversed the trajectory in Italy.

CONCLUSION

Mortality rate in Italy in the recent covid pandemic was higher mainly due to its unique demographic and socioeconomic profile. Italy being a western democracy, restrictions to daily liberties were difficult to enforce in a draconian fashion. Failure in the implementation of preventive strategies like social distancing was a major factor associated with increased infection rates in Italy. In addition, unpreparedness for the major pandemic by the health care system is yet another reason for the same. This review thus had highlighted the various flaws in the Italian administrative system to prevent the covid - 19 pandemic which is a lesson to be learnt by other countries to curb the major outbreaks in future.

AUTHOR CONTRIBUTIONS

Apurva choudhary
1. Execution of the work
2. Data collection
3. Drafting of manuscript

Smiline Girija AS
1. Concept and design of the study
2. Validation of the data collection
3. Revision and proofreading of the review

CONFLICT OF INTEREST

None to declare

REFERENCES

[1]   Anderson, R.M., Heesterbeek, H., Klinkenberg, D., and Hollingsworth, T.D. (2020) 'How Will Country-Based Mitigation Measures Influence the Course of the COVID-19 Epidemic?' The Lancet 395 (10228), 931–934

[2]   Ashwin, K.S. and Muralidharan, N.P. (2015) 'Vancomycin-Resistant Enterococcus (VRE) vs Methicillin-Resistant Staphylococcus Aureus (MRSA)'. in Indian Journal of Medical Microbiology [online] vol. 33 (5). 166. available from <http://dx.doi.org/10.4103/0255-0857.150976>

[3]   Backer, J.A., Klinkenberg, D., and Wallinga, J. (2020) 'Incubation Period of 2019 Novel Coronavirus (2019-nCoV) Infections among Travellers from Wuhan, China, 20-28 January 2020'. Euro Surveillance: Bulletin Europeen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin [online] 25 (5). available from <http://dx.doi.org/10.2807/1560-7917.ES.2020.25.5.2000062>

[4]   Bari, M.D., Di Bari, M., Balzi, D., Carreras, G., and Onder, G. (n.d.) Extensive Testing May Reduce COVID-19 Mortality: A Lesson from Northern Italy. available from <http://dx.doi.org/10.1101/2020.04.24.20078709>

[5]   Buja, A., Vianello, F.A., Zaccagnini, F., Pinato, C., and Maculan, P. (n.d.) Health Status of Female Moldovan Immigrants to Italy by Health Literacy Level and Age Group: A Descriptive Study. available from <http://dx.doi.org/10.21203/rs.3.rs-18825/v1>

[6]   Callaway, E. (2020) 'Time to Use the P-Word? Coronavirus Enters Dangerous New Phase'. in Nature [online] available from <http://dx.doi.org/10.1038/d41586-020-00551-1>

[7]   Chapman, J. and Webster, A. (2013) 'Faculty of 1000 Evaluation for Efficacy and Safety of Traditional Chinese Medicine (Shenqi Particle) for Patients With Idiopathic Membranous Nephropathy: A Multicenter Randomized Controlled Clinical Trial'. in F1000 - Post-Publication Peer Review of the Biomedical Literature [online] available from <http://dx.doi.org/10.3410/f.718025278.793484562>

[8]   Ciufolini, I. and Paolozzi, A. (2020) 'Mathematical Prediction of the Time Evolution of the COVID-19 Pandemic in Italy by a Gauss Error Function and Monte Carlo Simulations'. European Physical Journal plus 135 (4), 355

[9]   Francini, M., Gaudio, S., Palermo, A., and Viapiana, M.F. (2018) 'Pianificare La Resilienza Urbana Mediante I Piani Di Emergenza Di Protezione Civile'. in TERRITORIO [online] (85). 125–133. available from <http://dx.doi.org/10.3280/tr2018-085015>

[10] Frisan, T. (2020) 'Faculty Opinions Recommendation of Substantial Undocumented Infection Facilitates the Rapid Dissemination of Novel Coronavirus (SARS-CoV2)'. in Faculty Opinions – Post-Publication Peer Review of the Biomedical Literature [online] available from <http://dx.doi.org/10.3410/f.737557783.793572927>

[11] Girija As, S. and Priyadharshini J, V. (2019) 'CLSI Based Antibiogram Profile and the Detection of MDR and XDR Strains of Isolated from Urine Samples'. Medical Journal of the Islamic Republic of Iran 33, 3

[12] Girija, A.S.S., Smiline Girija, A.S., Shankar, E.M., and Larsson, M. (2020a) 'Could SARS-CoV-2-Induced Hyperinflammation Magnify the Severity of Coronavirus Disease (CoViD-19) Leading to Acute Respiratory Distress Syndrome?' in Frontiers in Immunology [online] vol. 11. available from <http://dx.doi.org/10.3389/fimmu.2020.01206>

[13] Girija, A.S.S., Smiline Girija, A.S., Shoba, G., and Vijayashree Priyadarshini, J. (2020b) 'Accessing the T-Cell and B-Cell Immuno-Dominant Peptides from A.baumannii Biofilm Associated Protein (bap) as Vaccine Candidates: A Computational Approach'. in International Journal of Peptide Research and Therapeutics [online] available from <http://dx.doi.org/10.1007/s10989-020-10064-0>

[14] Girija, A.S.S., Smiline Girija, A.S., Vijayashree Priyadarshini, J., and Paramasivam, A. (2019) 'Plasmid-Encoded Resistance to Trimethoprim/sulfamethoxazole Mediated by dfrA1, dfrA5, sul1 and sul2 among Acinetobacter Baumannii Isolated from Urine Samples of Patients with Severe Urinary Tract Infection'. in Journal of Global Antimicrobial Resistance [online] vol. 17. 145–146. available from <http://dx.doi.org/10.1016/j.jgar.2019.04.001>

[15] Girija, S.A.S., Jayaseelan, V.P., and Arumugam, P. (2018) 'Prevalence of VIM- and GIM-Producing Acinetobacter Baumannii from Patients with Severe Urinary Tract Infection'. in Acta Microbiologica et Immunologica Hungarica [online] vol. 65 (4). 539–550. available from <http://dx.doi.org/10.1556/030.65.2018.038>

[16] Grasselli, G., Pesenti, A., and Cecconi, M. (2020) 'Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response'. JAMA: The Journal of the American Medical Association [online] available from <http://dx.doi.org/10.1001/jama.2020.4031>

[17] Iosa, M., Paolucci, S., and Morone, G. (2020) 'Covid-19: A Dynamic Analysis of Fatality Risk in Italy'. Frontiers of Medicine 7, 185

[18] Iwasaki, A. and Grubaugh, N.D. (2020) 'Why Does Japan Have so Few Cases of COVID- 19?' in EMBO Molecular Medicine [online] vol. 12 (5). available from <http://dx.doi.org/10.15252/emmm.202012481>

[19] Kaly, L. and Rosner, I. (2012) 'Tocilizumab – A Novel Therapy for Non-Organ-Specific Autoimmune Diseases'. in Best Practice & Research Clinical Rheumatology [online] vol. 26 (1). 157–165. available from <http://dx.doi.org/10.1016/j.berh.2012.01.001>

[20]   Khaerunnisa, S., Kurniawan, H., Awaluddin, R., Suhartati, S., and Soetjipto, S. (n.d.) Potential Inhibitor of COVID-19 Main Protease (M[pro]) From Several Medicinal Plant Compounds by Molecular Docking Study. available from <http://dx.doi.org/10.20944/preprints202003.0226.v1>

[21]   Koh, G. (2020) 'Faculty Opinions Recommendation of Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)'. in Faculty Opinions – Post-Publication Peer Review of the Biomedical Literature [online] available from <http://dx.doi.org/10.3410/f.737509210.793572110>

[22]   Leung, C. (2020) 'Clinical Features of Deaths in the Novel Coronavirus Epidemic in China'. in Reviews in Medical Virology [online] vol. 30 (3). available from <http://dx.doi.org/10.1002/rmv.2103>

[23]   Lippi, G., Mattiuzzi, C., Sanchis- Gomar, F., and Henry, B.M. (2020) 'Clinical and Demographic Characteristics of Patients Dying from COVID- 19 in Italy vs China'. in Journal of Medical Virology [online] available from <http://dx.doi.org/10.1002/jmv.25860>

[24]   Li, R., Pei, S., Chen, B., Song, Y., Zhang, T., Yang, W., and Shaman, J. (2020) 'Substantial Undocumented Infection Facilitates the Rapid Dissemination of Novel Coronavirus (SARS-CoV-2)'. in Science [online] vol. 368 (6490). 489–493. available from <http://dx.doi.org/10.1126/science.abb3221>

[25]   Marickar, R.F., Geetha, R.V., and Neelakantan, P. (2014) 'Efficacy of Contemporary and Novel Intracanal Medicaments against Enterococcus Faecalis'. The Journal of Clinical Pediatric Dentistry 39 (1), 47–50

[26]   Mehta, P., McAuley, D.F., Brown, M., Sanchez, E., Tattersall, R.S., and Manson, J.J. (2020) 'COVID-19: Consider Cytokine Storm Syndromes and Immunosuppression'. in The Lancet [online] vol. 395 (10229). 1033–1034. available from <http://dx.doi.org/10.1016/s0140-6736(20)30628-0>

[27]   Michelozzi, P., de'Donato, F., Scortichini, M., De Sario, M., Noccioli, F., Rossi, P., and Davoli, M. (2020) 'Mortality Impacts of the Coronavirus Disease (COVID-19) Outbreak by Sex and Age: Rapid Mortality Surveillance System, Italy, 1 February to 18 April 2020'. in Eurosurveillance [online] vol. 25 (19). available from <http://dx.doi.org/10.2807/1560-7917.es.2020.25.19.2000620>

[28]   M, M.A., Geetha, R.V., and Thangavelu, L. (2019) 'Evaluation oEvaluation of Anti-Inflammatory Action of Laurus Nobilis-an in Vitro Study Of Anti-Inflammatory Action of Laurus Nobilis-an in Vitro Study'. in International Journal of Research in Pharmaceutical Sciences [online] vol. 10 (2). 1209–1213. available from <http://dx.doi.org/10.26452/ijrps.v10i2.408>

[29]   Mobaraki, K. and Ahmadzadeh, J. (2019) 'Current Epidemiological Status of Middle East Respiratory Syndrome Coronavirus in the World from 1.1.2017 to 17.1.2018: A Cross-Sectional Study'. in BMC Infectious Diseases [online] vol. 19 (1). available from <http://dx.doi.org/10.1186/s12879-019-3987-2>

[30]   Montacer, M. (n.d.) 'Social Distancing Effects of COVID-19 Pandemic Spread Lessons from Tunisia from March 3 to April 23, 2020'. in SSRN Electronic Journal [online] available from <http://dx.doi.org/10.2139/ssrn.3599535>

[31]   Moon, C. (2020) 'Fighting COVID-19 Exhausts T Cells'. Nature Reviews. Immunology 20 (5), 277

[32]   Onder, G., Rezza, G., and Brusaferro, S. (2020) 'Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy'. JAMA: The Journal of the American Medical Association [online] available from <http://dx.doi.org/10.1001/jama.2020.4683>

[33]   Paramasivam, A., Priyadharsini, J.V., and Raghunandhakumar, S. (2020) 'N6-Adenosine Methylation (m6A): A Promising New Molecular Target in Hypertension and Cardiovascular Diseases'. in Hypertension Research [online] vol. 43 (2). 153–154. available from <http://dx.doi.org/10.1038/s41440-019-0338-z>

[34]   Pasquariello, P. and Stranges, S. (n.d.) Excess Mortality from COVID-19: Lessons Learned from the Italian Experience. available from <http://dx.doi.org/10.20944/preprints202004.0065.v1>

[35]   Pratha, A.A., Ashwatha Pratha, A., and Geetha, R.V. (2017) 'Awareness on Hepatitis-B Vaccination among Dental Students-A Questionnaire Survey'. in Research Journal of Pharmacy and Technology [online] vol. 10 (5). 1360. available from <http://dx.doi.org/10.5958/0974-360x.2017.00240.2>

[36]   Priyadharsini, J.V., Vijayashree Priyadarshini, J., Smiline Girija, A.S., and Paramasivam, A. (2018a) 'An Insight into the Emergence of Acinetobacter Baumannii as an Oro-Dental Pathogen and Its Drug Resistance Gene Profile – An in Silico Approach'. in Heliyon [online] vol. 4 (12). e01051. available from <http://dx.doi.org/10.1016/j.heliyon.2018.e01051>

[37]   Priyadharsini, J.V., Vijayashree Priyadarshini, J., Smiline Girija, A.S., and Paramasivam, A. (2018b) 'In Silico Analysis of Virulence Genes in an Emerging Dental Pathogen A. Baumannii and Related Species'. in Archives of Oral Biology [online] vol. 94. 93–98. available from <http://dx.doi.org/10.1016/j.archoralbio.2018.07.001>

[38]   Rincon, M. and Irvin, C.G. (2012) 'Role of IL-6 in Asthma and Other Inflammatory Pulmonary Diseases'. in International Journal of Biological Sciences [online] vol. 8 (9). 1281–1290. available from <http://dx.doi.org/10.7150/ijbs.4874>

[39]   Rohlf, F.J., James Rohlf, F., and Swofford, D. (1989) 'Numerical Recipes: The Art of Scientific Computing. FORTRAN and Pascal Versions.William H. Press, Brian P. Flannery , Saul A. Teukolsky , William T. VetterlingNumerical Recipes Example Book. FORTRAN Version.William T. Vetterling , Saul A. Teukolsky , William H. Press, Brian P. FlanneryNumerical Recipes: The Art of Scientific Computing. FORTRAN and Pascal.Numerical Recipes Example Book. Pascal Version.William T. Vetterling , Saul A. Teukolsky , William H. Press, Brian P. FlanneryNumerical Recipes in C: The Art of Scientific Computing.William H. Press, Brian P. Flannery , Saul A. Teukolsky , William T. VetterlingNumerical Recipes Example Book (C).William T. Vetterling , Saul A. Teukolsky , William H. Press, Brian P. Flannery'. in The Quarterly Review of Biology [online] vol. 64 (1). 115–117. available from <http://dx.doi.org/10.1086/416228>

[40]   Rosenbaum, L. (2020) 'Facing Covid-19 in Italy — Ethics, Logistics, and Therapeutics on the Epidemic's Front Line'. in New England Journal of Medicine [online] vol. 382 (20). 1873–1875. available from <http://dx.doi.org/10.1056/nejmp2005492>

[41]   Ruan, Q., Yang, K., Wang, W., Jiang, L., and Song, J. (2020) 'Clinical Predictors of Mortality due to COVID-19 Based on an Analysis of Data of 150 Patients from Wuhan, China'. in Intensive Care Medicine [online] vol. 46 (5). 846–848. available from <http://dx.doi.org/10.1007/s00134-020-05991-x>

[42]   Selvakumar, R. and Np, M. (2017) 'COMPARISON IN BENEFITS OF HERBAL MOUTHWASHES WITH CHLORHEXIDINE MOUTHWASH: A REVIEW'. in Asian Journal of Pharmaceutical and Clinical Research [online] vol. 10 (2). 3. available from <http://dx.doi.org/10.22159/ajpcr.2017.v10i2.13304>

[43]   Shahana, R.Y. and Muralidharan, N.P. (2016) 'Efficacy of Mouth Rinse in Maintaining Oral Health of Patients Attending Orthodontic Clinics'. in Research Journal of Pharmacy and Technology [online] vol. 9 (11). 1991. available from <http://dx.doi.org/10.5958/0974-360x.2016.00406.6>

[44]   Shimabukuro-Vornhagen, A., Gödel, P., Subklewe, M., Stemmler, H.J., Schlößer, H.A., Schlaak, M., Kochanek, M., Böll, B., and von Bergwelt-Baildon, M.S. (2018) 'Cytokine Release Syndrome'. Journal for Immunotherapy of Cancer 6 (1), 56

[45]   Sjödin, H., Wilder-Smith, A., Osman, S., Farooq, Z., and Rocklöv, J. (2020) 'Only Strict Quarantine Measures Can Curb the Coronavirus Disease (COVID-19) Outbreak in Italy, 2020'. in Eurosurveillance [online] vol. 25 (13). available from <http://dx.doi.org/10.2807/1560-7917.es.2020.25.13.2000280>

[46]   Smiline, A.S.G., Vijayashree, J.P., and Paramasivam, A. (2018) 'Molecular Characterization of Plasmid-Encoded blaTEM, blaSHV and blaCTX-M among Extended Spectrum β-Lactamases [ESBLs] Producing Acinetobacter Baumannii'. in British Journal of Biomedical Science [online] vol. 75 (4). 200–202. available from <http://dx.doi.org/10.1080/09674845.2018.1492207>

[47]   Sterpetti, A.V. (2020) 'Lessons Learned During the COVID-19 Virus Pandemic'. Journal of the American College of Surgeons 230 (6), 1092–1093

[48]   Tanaka, T., Narazaki, M., and Kishimoto, T. (2016) 'Immunotherapeutic Implications of IL-6 Blockade for Cytokine Storm'. in Immunotherapy [online] vol. 8 (8). 959–970. available from <http://dx.doi.org/10.2217/imt-2016-0020>

[49] Tisoncik, J.R., Korth, M.J., Simmons, C.P., Farrar, J., Martin, T.R., and Katze, M.G. (2012) 'Into the Eye of the Cytokine Storm'. in Microbiology and Molecular Biology Reviews [online] vol. 76 (1). 16–32. available from <http://dx.doi.org/10.1128/mmbr.05015-11>

[50]   Tseng, C.-T.K., Perrone, L.A., Zhu, H., Makino, S., and Peters, C.J. (2005) 'Severe Acute Respiratory Syndrome and the Innate Immune Responses: Modulation of Effector Cell Function without Productive Infection'. in The Journal of Immunology [online] vol. 174 (12). 7977–7985. available from <http://dx.doi.org/10.4049/jimmunol.174.12.7977>

[51] Vaishali, M. and Geetha, R.V. (2018) 'Antibacterial Activity of Orange Peel Oil on Streptococcus Mutans and Enterococcus-An In-Vitro Study'. in Research Journal of Pharmacy and Technology [online] vol. 11 (2). 513. available from <http://dx.doi.org/10.5958/0974-360x.2018.00094.x>

[52] Wang, W., Tang, J., and Wei, F. (2020) 'Updated Understanding of the Outbreak of 2019 Novel Coronavirus (2019- nCoV) in Wuhan, China'. in Journal of Medical Virology [online] vol. 92 (4). 441–447. available from <http://dx.doi.org/10.1002/jmv.25689>

[53] Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, Xing, Xu, S., Huang, H., Zhang, L., Zhou, Xia, Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, Xin, Chen, D., Xiong, W., Xu, L., Zhou, F., Jiang, J., Bai, C., Zheng, J., and Song, Y. (2020) 'Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China'. in JAMA Internal Medicine [online] available from <http://dx.doi.org/10.1001/jamainternmed.2020.0994>

[54] Ye, Q., Wang, B., and Mao, J. (2020) 'The Pathogenesis and Treatment of the `Cytokine Storm' in COVID-19'. in Journal of Infection [online] vol. 80 (6). 607–613. available from <http://dx.doi.org/10.1016/j.jinf.2020.03.037>

Figure 1: An overview on the exorbitant increase in the mortality rate in the recent n-CoV pandemic in Italy

Figure 1 : Total Coronavirus deaths