Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Highlights

One day at a time

Aila Akosua Kattner[*]

Freelance Journalist, Berlin, Germany

ARTICLE INFO

Article history:
Available online 15 January 2022

Keywords:
SARS-CoV-2
HIV
Awake craniotomy
IRES
Cancer
Emergency endotracheal intubation

ABSTRACT

In this issue of *Biomedical Journal* we get to know measures to prevent a nosocomial COVID-19 outbreak, a compound that is able to stall SARS-CoV-2 replication, and the connection between air pollution and COVID-19 cases. Another article allows an insight into the potential of treating HIV combining a conventional drug and low level laser therapy. Furthermore, the advantages of awake craniotomy are presented, the efficacy of IRES is examined, and plant extracts are on the one hand explored as a nociceptive agent and on the other hand as therapeutic approach against breast cancer. We learn about drug resistance in liver cancer, a mutation involved in a rare inflammatory disorder, and lung surgery related unilateral vocal fold paralysis. Finally, the success of emergency endotracheal intubations across different hospital units is compared, the importance of monitoring cerebral blood flow in asphyxiated neonates is elucidated, and resistance variants in hepatitis C virus are examined. A study about the necessity to perform quantitative cardiac MRI in Asian population is presented, and an approach is shown on how to augment the effect of platelet-rich plasma injections in chronic knee osteoarthritis.

Spotlight

Almost one year after being declared a pandemic by the WHO,[1] COVID-19 still heavily influences our daily life. Understanding the transmission dynamics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well accurate data on incubation time and secondary attack rate are key in managing containment [1]. Although the basic reproduction number R0 had originally been estimated to be around 2 in Wuhan, China, this value might be strongly influenced by specific situations and settings driving the outbreak [2]. Social habits, population density and accordingly contact between citizens are some examples that exert an impact on R0 [3]. The secondary attack rate is defined as the probability of an infection occurring in susceptible people within a specific group like household members or close contacts [2]. It has been observed that public health measures like rapid contact tracing reduce R0 significantly, although contact tracing can be resource intensive (see Fig. 1). Singapore, China and Korea were thus able to limit the size of initial outbreaks by identifying new cases before symptom onset [4].

Virus containment in a hospital

Especially when the available space is restricted and a multitude of people come together on a daily basis, effective measures to reduce spreading of COVID-19 need to be put in place. Cheng and colleagues report on the advance deployment of

* Corresponding author. Freelance Journalist, Berlin, Germany.
E-mail address: aila.kattner@gmail.com.
Peer review under responsibility of Chang Gung University.

[1] https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov), last access 12/28/2021.

https://doi.org/10.1016/j.bj.2022.01.009

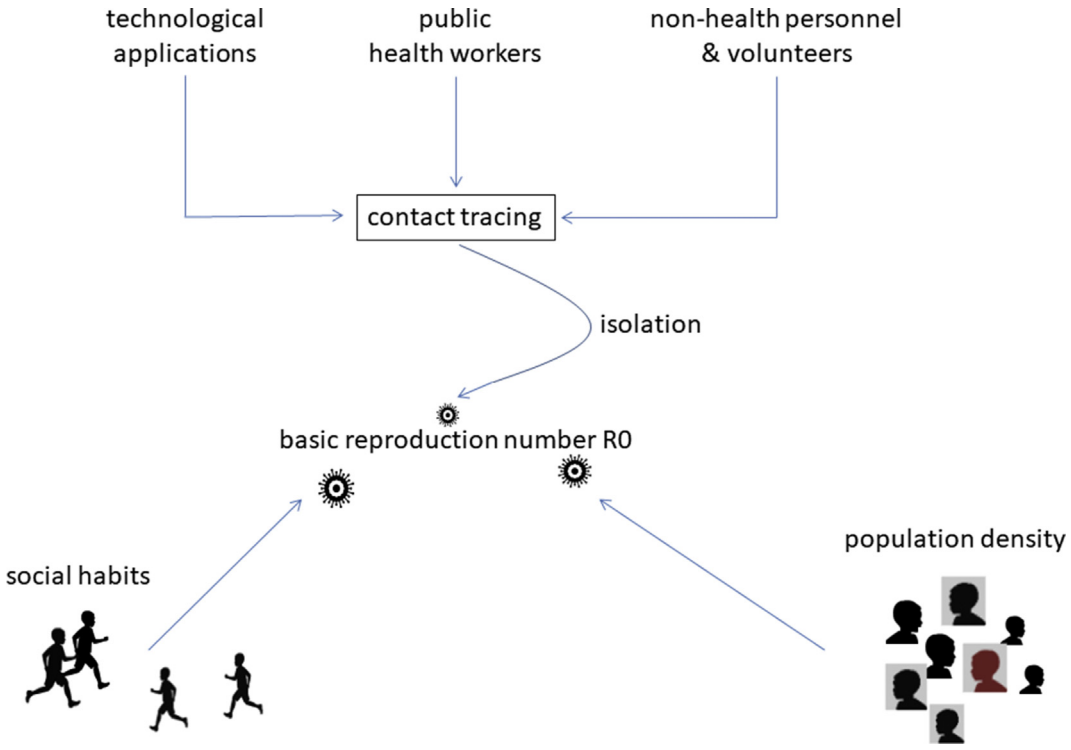

Fig. 1 Local differences in social habits and population density versus the implementation and available resources to conduct rigorous contact tracing were some of the cornerstones that led to geographical variety in the basic reproduction number R0 for COVID-19 outbreaks.

control measures to prevent nosocomial outbreaks of COVID-19 in a Taiwanese hospital. Their results suggest that implementation of reinforced dynamic infection control policies, efficient diagnostic testing and response allow to keep up the function and capacity of the health care system under duress of the pandemic [5].

Stalling SARS-CoV-2

Also, the urgency of the pandemic situation drives the search for new treatment approaches on several levels. Targeting the viral replication machinery is one of them. SARS-CoV-2 makes use of an RNA-dependent RNA polymerase (RdRp) for genome replication and gene transcription. The RdRp consists of three viral protein subunits, one of them being the non-structural protein 12 (nsp12). The active-site cleft of this catalytical subunit is responsible for binding to the first turn of RNA and mediates RdRp activity with conserved residues [6].

The FDA-approved drug remdesivir used for treating COVID-19 patients inhibits the RdRp of coronaviruses. The mechanism involves incorporation of remdesivir into the growing RNA which induces delayed RdRp stalling, caused by a sterical translocation barrier. Nevertheless some proof-reading can occur, rendering remdesivir less efficient [7].

Xia et al. performed a molecular docking study to predict the binding of various lipopeptides to the central component of viral replication and transcription, nsp12. They found seven lipopeptides that bind to nsp12 at the same location as remdesivir but with even higher affinity. Ferrocin A-iron complex was binding most tightly. The iron chelating peptide hence offers a novel basis for developing treatments against coronavirus [8].

Poor air quality and COVID-19

Another question relates to the role environmental factors might have played in the number of COVID-19 cases. Air quality for instance improved in 2020 in most countries as a result of lockdown measures. On the other hand wildfires and severe burning of fossil fuels counterbalanced the dip in air pollution in some regions.[2] The primary contributor to air pollution is particular matter (PM). Upon inhalation, PM interacts with pulmonary surfactant, thus negatively impacting the role of surfactant in alveolar stability and immune modulation. Short-term exposure to PM causes acute inflammatory responses in the airways, whereas long-term exposure correlates with mortality of cardiovascular disease as well as lung cancer [9].

Czwojdzińska et al. examined the connection between atmospheric contamination and the number of COVID-19 cases in Poland over the duration of one year. In recent years, Poland had recorded the highest annual average concentration of fine and coarse PM in Europe. In contrast to studies performed in other countries, the research team concludes that the distribution of COVID-19 incidents was independent from the annual levels of PM concentrations in Poland. They also suggest that a change in lifestyle due to lockdowns across various

[2] https://www.iqair.com/blog/press-releases/covid-19-reduces-air-pollution-in-most-countries, last access 12/28/2021.

seasons needs to be taken in account and air pollution has to be measured in real time as opposed to relying on archival data as other researchers have done in the past. However, Czwojdzińska et al. also acknowledge that the accuracy of their study might have suffered due to underreporting of COVID-19 cases [10].

Also in this issue

Seeing the light of day

Low level laser therapy (LLLT) or photobiomodulation had been first introduced in its modern form in the 1960s. Currently LLLT is used to reduce inflammation, edema, chronic joint disorders, in order to promote healing of wounds, deeper tissues, nerves and also for treatment of neurological disorders and pain [11]. However, still in the early 2000s LLLT had been considered as charlatanry by some authorities. This might have been due to a variety in treatment outcomes caused by a number of protocols with different parameters as to light source, wavelength, power density, pulse structure, fluence etc. Research studies like for instance the identification of cytochrome c oxidase as primary chromophore in the mitochondrial respiratory chain led to a change in perception of LLLT treatment [12].

Absorption of laser light leads to the desired effect of tissue interaction. It is suggested that LLLT acts on the chromophores in mitochondria, increasing ATP production, modulating reactive oxygen species and inducing transcription factors. Especially also immune cells seem to be positively affected by LLLT [11].

Lugongolo and her research team set out for an *in vitro* study to examine the effect of LLLT combined with efavirenz on human immunodeficiency virus (HIV). The use of both, the reverse transcriptase inhibitor in addition to LLLT, entailed a reduction in HIV infection. Lugongolo et al. suggest that further investigation could lead to the development of a portable device for treating individuals with HIV at home or in hospitals [13].

The extraction of the stone of madness[3]

Trephination has been performed across the world since the Neolithic period. An examination of skulls from the medieval period in Germany suggests that the mortality and infection rates for trepanation were low, some skulls showed clear evidence of survival and healing after the procedure [14].

Nowadays, awake craniotomy has been increasingly popular for minimally invasive procedures and moreover for mapping and resecting lesions in vitally important parts of the brain. With the patient awake during a part of the surgery, tumor resection can be maximized while preserving neurological function [15].

In a retrospective study Li et al. evaluate the outcome in 225 patients with recurrent glioma undergoing awake craniotomy in comparison to conservative general anesthesia craniotomy. The research team finds that awake craniotomy leads to a better general performance postoperatively as well as a reduction in late neurological deficits [16]. Additionally, the need for postoperative intensive care, monitoring and length of hospital stays are reduced [15].

Efficacy of IRES

Internal ribosomal entry sites (IRES) have first been discovered in 1988 in the naturally uncapped poliovirus RNA [17] and in encephalomyocarditis virus (EMCV) RNA [18]. IRES are translational enhancers mediating internal initiation of translation when present between genes of interest, thus allowing multicistronic expression cassettes resembling bacterial operons. IRES-based vectors are successfully used in preclinical and clinical assays of combined gene therapy for various purposes including transgene and fluorescent reporter molecules [19]. However, the efficiency of an IRES in bicistronic gene expression depends on factors like its sequence and gene location [20].

Shen et al. examined the differences in translational efficacy between cap-dependent upstream and downstream cistrons of EMCV IRES with quantifiable reporter genes. They observed EMCV IRES being relatively less efficient than cap-dependent translation depending of target gene location. Lower protein yield was obtained when the reporter gene was located downstream of the IRES. An even more substantial reduction in protein production was observed when an upstream cistron was present [21].

South American Whitebrush as antinociceptive agent

Traditionally, tea made from *Aloysia gratissima* leaves has been used in South America to treat various digestive and respiratory issues, neuralgia and insomnia.[4] It is furthermore indicated that the oil possesses antidepressant like effects [22].

Souza et al. explored in detail the analgesic and sedative abilities of the plant extract in mice. The team subjected *A. gratissima* leaves to extraction with supercritical CO_2 and proved that the extract exerts an antinociceptive effect, mediated by ATP sensitive K^+ channels. They suggest this effect to be caused by terpene compounds in the leaves [23].

Drug resistance in liver cancer

Liver cancer was the third most common cause of cancer death in 2020.[5] A therapeutic approach for hepatocellular carcinoma (HCC), the most common type of primary liver cancer, includes the multikinase inhibitor sorafenib. The drug exerts antiproliferative and antiangiogenic effects on tumor growth, however, acquired drug resistance diminishes the therapeutic efficacy [24]. In 2012 the drug had also received great attention, but for different reasons: in return for 6% royalties the Indian

[3] https://www.museodelprado.es/en/the-collection/art-work/the-extraction-of-the-stone-of-madness/313db7a0-f9bf-49ad-a242-67e95b14c5a2, last access 12/25/2021

[4] https://www.mundoecologia.com.br/plantas/cha-de-alfazema-do-brasil-beneficios-como-preparar-e-fazer/, last access 12/28/2021.

[5] https://www.who.int/news-room/fact-sheets/detail/cancer, last access 12/28/21.

Patent Office allowed in a court landmark ruling domestic firms to sell a generic version of the patent-protected drug from German company Bayer. The compulsory license, that also overcomes international trade rules, had been issued because Bayer had not made the drug reasonably affordable in India. The price of the generic drug was set to be 31 times lower than that of the original anti-cancer drug.[6,7]

Yu and team investigated the responses of 23 HCC patients treated with sorafenib. They found that sorafenib resistance in the cohort was associated with a high percentage genome change and amplification of chromosome 7q in advanced HCC. Treatment success with sorafenib could hence potentially be predicted through analyzing tumor specimen of patients before drug administration [25].

A natural flavonoid against breast cancer

Since natural compounds are perceived as safer in terms of side effects in comparison to chemical drugs, the interest in using phytochemicals for pharmacological therapeutics has sparked in recent years. A compound that has been drawing attention to it because of its powerful anti-cancer effects is pristimerin, a triterpenoid extracted from *Celastracea* and *Hippocrateaceae* [26,27].

Liu et al. examined the effect of pristimerin on the epithelial–mesenchymal transition (EMT) in breast cancer cells. Their results showed that the natural flavonoid compound exerts an inhibitory effect on cell-proliferation that is dose-dependent and effective in even relatively low concentrations. Furthermore, in a mouse xenograft model pristimerin inhibits and reverses EMT through impacting integrin β3, a transmembrane receptor playing an important role in the development of tumor invasion and metastasis [28]. The promising clinical application of pristimerin will require further research, at the same time new approaches will be required to produce the triterpene extracts in an environmentally friendly and efficient way at industrial level [29].

The Power of Rare

Neuromyelitis optica spectrum disorder (NMOSD) is a rare inflammatory disorder mediated by antibodies against Aquaporin 4 (AQP4). AQP4 is the most ubiquitous water channel in the central nervous system (CNS) and expressed on astrocytes. Although AQP4 is also present in the kidneys, stomach, airways, secretory glands and skeletal muscle, those tissues are protected from antibody led damage thanks to local inhibitors which are not present in the brain. Untreated, half of NMOSD patients will become wheelchair users and blind, a third will have died within five years of their first attack [30]. In the past, NMOSD used to have a poor prognosis, however, current treatment approaches focusing on preventing attacks and relapses have improved long-term treatment results [31]. NMOSD occurs more frequently in women than men, and disproportionally more frequent in Asian and AfricanAmerican populations [32].

Huang et al. set out to have a closer look at the genetic factors that may be involved in NMOSD and performed a whole exome sequencing study in a small Taiwanese cohort. They discovered a mutation in an exon of the CD33 gene, which is believed to be involved in modulating inflammatory and immune responses. The CD33 frameshift variant is ethnicity-specific for East Asian populations according to the gnomAD database [33].

The Power of Rare: A Blueprint for a Medical Revolution is a book by Victoria Jackson, who founded the Guthy-Jackson Charitable Foundation in 2008 after her daughter had been diagnosed with NMOSD. The foundation is dedicated to finding a cure for NMOSD, connecting hundreds of researchers, clinicians and private persons from more than 30 countries for the cause.[8,9]

Part of Your World

The famous bass-baritone singer George London (1920–1985) was the first North American singer to perform at Bolshoi Theater in Moscow in 1960, a performance for which he received standing ovations, saying afterwards: "This is the climax of a life's dream [34]. However, already in this year he encountered first vocal disturbances, leading to him retiring prematurely from singing at age 47. It has been suggested that he suffered from unilateral vocal fold paralysis (UVFP). During London's era UVFP was thought to be originating from viral hepatitis, although Duek et al. suggest a previous laryngitis and following post-viral neuropathy as underlying cause [35].

It is known now, that vocal fold paralysis may result after surgery, central nervous system disorders, radiation induced cranial nerve paralysis and neck cancer [36].

Chang et al. compare in a retrospective study UVFP caused by lung surgery to characteristics of UVFP caused by esophageal and thyroid surgeries. They find that lung surgery related UVFP presents in a distinct manner and recovery of voice parameters can be facilitated through administration of hyaluronate injection [37].

The song Part of Your World is the closing song in the Broadway spectacle "The Little Mermaid" when Ariel regains her voice.[10]

Emergency endotracheal intubation across different hospital units

Due to potentially high complications, emergency endotracheal intubation are challenging under controlled conditions as for instance in the operating room (OR). However, airway management outside the OR inherently entails an even additional number of unpredictable factors [38].

Especially in the current time of the COVID-19 pandemic, the success of emergency intubations depends on establishing institutional guidelines, preparation and practice drills to

[6] https://www.nature.com/articles/483250a, last access 12/28/2021.

[7] https://www.pmlive.com/pharma_news/bayer_fails_to_overturn_nexavar_compulsory_licence_in_india_466101, last access 12/28/2021.

[8] https://guthyjacksonfoundation.org/about-us/, last access 12/25/2021.

[9] https://guthyjacksonfoundation.org/gjcf-10-years/, last access 12/25/2021.

[10] https://little-mermaid.fandom.com/wiki/Part_of_Your_World_(Finale), last access 12/28/2021.

mitigate possible complications and enhance safety of the health care personnel [39].

Hsiao et al. evaluated the outcome of a total of 416 emergency endotracheal intubations in the general ward, the intensive care unit (ICU) and the emergency department (ED) in 2015 and 2016 in a tertiary care facility. Emergency intubations in the ICU and general ward were less successful than those performed in the ED, calling in an anesthesiologist especially in the case of difficult intubations in the ED led to a higher rate of neurologically intact survival [40].

Monitoring asphyxiated neonates

Cerebrovascular pressure autoregulation constitutes a vital protective mechanism of the brain in order to maintain a relatively constant cerebral blood flow (CBF). Impairments in the autoregulation increase the risk of brain injury and neurological disabilities, and especially infants are highly sensitive to changes in CBF [41]. Perinatal asphyxia may lead to alterations in CBF, hence close monitoring of the neonatal cerebral circulation is required in the case thereof [42].

Ho et al. conducted a retrospective cohort study in the neonatal ICU, assessing the correlation between middle cerebral artery (MCA) flow velocity and the severity of hypoxic ischemic encephalopathy (HIE) in neonates who received therapeutic hypothermia (TH) [43]. TH has been introduced in 2010 in Taiwan as a treatment for HIE newborn patients and consensus recommendations were determined in 2015 [44]. Ho et al. concluded that mean flow velocity in MCA is correlated to the severity of MRI brain injury. The team suggests the use of transcranial Doppler sonography as a potential predictive tool for neurodevelopmental outcomes during the first days in asphyxiated neonates [43].

Resistance associated variants in HCV

Since 2011 a new therapeutic approach against hepatitis C virus (HCV) has been approved in the form of direct-acting antivirals (DAA). A new generation of DAAs, that then came two years later, turned out to be even more effective by increasing rates of sustained viral response up to 100% while at the same time proving to be less toxic and more tolerable than the conventional combination strategy of pegylated interferon and ribavirin [45]. DAAs revolutionized patient care by targeting the replication cycle of HCV, resulting in progressively shorter durations of treatment, mainly in patients without comorbidities. A pitfall of DAAs lies in the emergence of drug-resistant HCV variants [46]. The mutations occur in the non-structural (NS) proteins 5A and 5B of the HCV genome and the specific resistance associated variants (RAVs) depend on the virus subtype as well as geography [47].

In a retrospective, single-center cohort study Tsai et al. determined the prevalence of NS5A RAVs in Taiwanese HCV-infected patients, advocating for taking mutated HCV variants into consideration before using NS5A inhibitors [48].

Cardiovascular health parameters in Taiwanese population

When evaluating the output of magnetic resonance imaging (MRI), tissues can be characterized by two different relaxation times T1 and T2, respectively longitudinal relaxation time (rate at which excited protons return to equilibrium) and transverse relaxation time (time until spinning protons lose phase coherence).[11]

The timely assessment of myocardial tissue health is essential because of the low capacity in myocardial regeneration. A method to perform a quantitative mapping is through cardiac MRI (CMRI). Tsai et al. emphasize the need to evaluate the relationship between clinical parameters and quantitative mapping from CMRI in Asian population as the relaxation time in healthy myocardium has been previously reported for Caucasian population only. Tsai's and colleagues' retrospective study in 93 healthy, Taiwanese participants summarizes the cohort specific relaxation times and furthermore positive and negative correlations between ejection fraction and pulse rate to relaxation times in dependence of age and gender [49].

Vampire facial

Platelet-rich plasma (PRP) injections have won in popularity due to their range of possible applications for medical and cosmetic purposes while at the same time involving few side effects and a low risk procedure. The term "vampire facial" for instance refers to the use of autologous PRP for rejuvenating skin by reducing wrinkles, scars and sun damage in facial areas,[12] although the technique is then often used in combination with laser treatments, dermal fillers or microneedling to significantly improve skin appearance, texture and tone [50].

PRP has proven to be promising for treating various musculoskeletal disorders and especially supports the repair of tissues with poor healing capacity like tendons, cartilage and ligaments. PRP is hence used for therapeutic purposes in the case of osteoarthritis of knee and hip, plantar fasciitis, lateral epicondylitis, rotator cuff tendinopathy and patellar tendinopathy [51]. The positive effect of PRP is based on the platelet growth factors that support the phases of wound healing. However, preparation protocols vary strongly, leading to inconsistencies in patient outcomes [52].

For treatment of chronic knee osteoarthritis (KO), ultrasound or fluoroscopy guided genicular nerve block successfully alleviate pain and improve knee function [53].

In a single-blinded, case-controlled study Chen and team explored the proteomic changes in synovial fluid in between and after PRP injections either in combination with saline or 5% dextrose water in genicular nerve blocks in elderly patients. The addition of dextrose augments the positive effect of PRP in treating KO, and thus constitutes a feasible treatment option for patients who are looking for a non-surgical, conservative treatment option [54].

Conflicts of interest

The author declares no conflict of interests.

[11] https://case.edu/med/neurology/NR/MRI%20Basics.htm, last access 12/25/2021.

[12] https://health.clevelandclinic.org/can-a-vampire-facial-make-you-look-younger/, last access 12/25/2021.

REFERENCES

[1] Rybniker J, Fätkenheuer G. Importance of precise data on SARS-CoV-2 transmission dynamics control. Lancet Infect Dis 2020;20:877–9.
[2] Liu Y, Eggo RM, Kucharski AJ. Secondary attack rate and superspreading events for SARS-CoV-2. Lancet 2020;395:e47.
[3] Locatelli I, Trächsel B, Rousson V. Estimating the basic reproduction number for COVID-19 in Western Europe. PLoS One 2021;16:e0248731.
[4] Koçak C. COVID-19 isolation and contact tracing with country samples: a systematic review. Iran J Public Health 2021;50:1547–54.
[5] Cheng CW, Huang PY, Wu TS, Huang CG, Tsao KC, Lin CS, et al. Infection control operations of a large hospital in Taiwan to prevent nosocomial outbreaks during COVID-19 pandemic. Biomed J 2021;44:S8–14.
[6] Hillen HS, Kokic G, Farnung L, Dienemann C, Tegunov D, Cramer P. Structure of replicating SARS-CoV-2 polymerase. Nat 2020;584:154–6.
[7] Kokic G, Hillen HS, Tegunov D, Dienemann C, Seitz F, Schmitzova J, et al. Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. Nat Commun 2021;12:279.
[8] Xia B, Luo M, Pang L, Liu X, Yi Y. Lipopeptides against COVID-19 RNA-dependent RNA polymerase using molecular docking. Biomed J 2021;44:S15–24.
[9] Wang F, Liu J, Zeng H. Interactions of particulate matter and pulmonary surfactant: implications for human health. Adv Colloid Interface Sci 2020;284:102244.
[10] Czwojdzińska M, Terpińska M, Kuźniarski A, Płaczkowska S, Piwowar A. Exposure to PM2.5 and PM10 and COVID-19 infection rates and mortality: a one-year observational study in Poland. Biomed J 2021;44:S25–36.
[11] Chung H, Dai T, Sharma SK, Huang YY, Carroll JD, Hamblin MR. The nuts and bolts of low-level laser (light) therapy. Ann Biomed Eng 2012;40:516–33.
[12] Hamblin MR. Photobiomodulation or low-level laser therapy. J Biophotonics 2016;9:1122–4.
[13] Lugongolo MY, Manoto SL, Ombinda-Lemboumba S, Maaza M, Mthunzi-Kufa P. The combination of low level laser therapy and efavirenz drastically reduces HIV infection in TZM-bl cells. Biomed J 2021;44:S37–47.
[14] Weber J, Czarnetzki A. Trepanationen im frühen mittelalter im südwesten von Deutschland – Indikationen, komplikationen und outcome. Zentralblatt Neurochir 2001;62:10–4.
[15] Zhang K, Gelb AW. Awake craniotomy: indications, benefits, and techniques. Colomb J Anesthesiol 2018;46:46–51.
[16] Li YC, Chiu HY, Wei KC, Lin YJ, Chen KT, Hsu PW, et al. Using cortical function mapping by awake craniotomy dealing with the patient with recurrent glioma in the eloquent cortex. Biomed J 2021;44:S48–53.
[17] Pelletier J, Sonenberg N. Internal initiation of translation of eukaryotic mRNA directed by a sequence derived from poliovirus RNA. Nature 1988;334:320–5.
[18] Jang SK, Krausslich HG, Nicklin MJH, Duke GM, Palmenberg AC, Wimmer E. A segment of the 5′ nontranslated region of encephalomyocarditis virus RNA directs internal entry of ribosomes during in vitro translation. J Virol 1988;62:2636–43.
[19] Renaud-Gabardos E, Hantelys F, Morfoisse F, Chaufour X, Garmy-Susini B, Prats AC. Internal ribosome entry site-based vectors for combined gene therapy. World J Exp Med 2015;5:11–20.
[20] Bochkov YA, Palmenberg AC. Translational efficiency of EMCV IRES in bicistronic vectors is dependent upon IRES sequence and gene location. Biotechniques 2006;41:283–4. 286, 288 passim.
[21] Shen CR, Chen YS, Hwang YS, Chen HJ, Liu CL. Differential bicistronic gene translation mediated by the internal ribosome entry site element of encephalomyocarditis virus. Biomed J 2021;44:S54–62.
[22] Zeni AL, Zomkowski AD, Maraschin M, Tasca CI, Rodrigues AL. Evidence of the involvement of the monoaminergic systems in the antidepressant-like effect of *Aloysia gratissima*. J Ethnopharmacol 2013;148:914–20.
[23] Souza MA, Scapinello J, Guzatti JGG, Scatolin M, Martello R, Schindler MSZ, et al. Antinociceptive effect and mechanism of supercritical carbon dioxide extract of *Aloysia gratissima* leaves in mice. Biomed J 2021;44:S63–72.
[24] Xia S, Pan Y, Liang Y, Xu J, Cai X. The microenvironmental and metabolic aspects of sorafenib resistance in hepatocellular carcinoma. EBioMedicine 2020;51:102610.
[25] Yu MC, Wu TH, Lee CW, Lee YS, Lian JH, Tsai CL, et al. Percentage genome change and chromosome 7q amplification predict sorafenib response in advanced hepatocellular carcinoma. Biomed J 2021;44:S73–83.
[26] Li JJ, Yan YY, Sun HM, Liu Y, Su CY, Chen HB, et al. Anti-cancer effects of pristimerin and the mechanisms: a critical review. Front Pharmacol 2019;10:746.
[27] Seo HW, Park JH, Lee JY, Park HJ, Kim JK. Pristimerin, a naturally occurring triterpenoid, exerts potent anticancer effect in colon cancer cells. Biomed Sci Lett 2018;24:15–22.
[28] Liu S, Dong Y, Wang Y, Hu P, Wang J, Wang RY. Pristimerin exerts antitumor activity against MDA-MB-231 triple-negative breast cancer cells by reversing of epithelial-mesenchymal transition via downregulation of integrin β3. Biomed J 2021;44:S84–92.
[29] González-Félix MA, Mejía-Manzano LA, Barba-Dávila BA, Serna-Saldívar SO, González-Valdez J. Optimized and scalable green extraction of pristimerin, an anticancerigen from *Mortonia greggii*, by ethanol–phosphate aqueous two-phase systems. Ind Eng Chem Res 2021;60:5403–10.
[30] Huda S, Whittam D, Bhojak M, Chamberlain J, Noonan C, Jacob A. Neuromyelitis optica spectrum disorders. Clin Med 2019;19:169–76.
[31] Jarius S, Paul F, Weinshenker BG, Levy M, Kim HJ, Wildemann B. Neuromyelitis optica. Nat Rev Dis Prim 2020;6:85.
[32] Pittock SJ, Lucchinetti CF. Neuromyelitis optica and the evolving spectrum of autoimmune aquaporin-4 channelopathies: a decade later. Ann N Y Acad Sci 2016;1366:20–39.
[33] Huang YJ, Lee JJ, Fan WL, Hsu CW, Tsai NW, Lu CH, et al. A CD33 frameshift variant is associated with neuromyelitis optica spectrum disorders. Biomed J 2021;44:S93–100.
[34] London N. George London: of gods and demons. US: Baskerville Publishers; 2005.
[35] Duek I, Cohen JT, Gil Z. Unilateral vocal cord paralysis of a great Jewish opera singer. Rambam Maimonides Med J 2018;9:e0009.
[36] Wang HW, Lu CC, Chao PZ, Lee FP. Causes of vocal fold paralysis. Ear Nose Throat J 2020 Oct:145561320965212.
[37] Chang TL, Fang TJ, Wong AMK, Wu CF, Pei YC. Clinical and functional characteristics of lung surgery-related vocal fold palsy. Biomed J 2021;44:S101–9.
[38] Mechlin MW, Hurford WE. Emergency tracheal intubation: techniques and outcomes. Respir Care 2014;59:881–92.
[39] Shrestha GS, Shrestha N, Lamsal R, Pradhan S, Shrestha A, Canelli R, et al. Emergency intubation in covid-19. N Engl J Med 2021;384:e20.

[40] Hsiao YJ, Chen CY, Hung HT, Lee CH, Su YY, Ng CJ, et al. Comparison of the outcome of emergency endotracheal intubation in the general ward, intensive care unit and emergency department. Biomed J 2021;44:S110–8.
[41] Rhee CJ, da Costa CS, Austin T, Brady KM, Czosnyka M, Lee JK. Neonatal cerebrovascular autoregulation. Pediatr Res 2018;84:602–10.
[42] Yoshida-Shuto H, Yasuhara A, Kobayashi Y. Cerebral blood flow velocity and failure of autoregulation in neonates: their relation to outcome of birth asphyxia. Neuropediatrics 1992;23:241–4.
[43] Ho SY, Chiang MC, Lin JJ, Chou IJ, Lee CC, Diane Mok TY, et al. Middle cerebral artery velocity is associated with the severity of MRI brain injury in neonates received therapeutic hypothermia. Biomed J 2021;44:S119–25.
[44] Chiang MC, Jong YJ, Lin CH. Therapeutic hypothermia for neonates with hypoxic ischemic encephalopathy. Pediatr Neonatol 2017;58:475–83.
[45] González-Grande R, Jiménez-Pérez M, González Arjona C, Mostazo Torres J. New approaches in the treatment of hepatitis C. World J Gastroenterol 2016;22:1421–32.
[46] Baumert TF, Berg T, Lim JK, Nelson DR. Status of direct-acting antiviral therapy for hepatitis C virus infection and remaining challenges. Gastroenterology 2019;156:431–45.
[47] Jones BR, Howe AYM, Harrigan PR, Joy JB. The global origins of resistance-associated variants in the non-structural proteins 5A and 5B of the hepatitis C virus. Virus Evol 2018;4:vex041.
[48] Tsai MC, Hung CH, Lu SN, Wang JH, Chen CH, Kee KM, et al. The incidence of resistance-associated variants to NS5A in HCV subtypes 1a and 1b in Taiwan. Biomed J 2021;44:S126–31.
[49] Tsai CC, Ng SH, Chen YL, Juan YH, Wang CH, Lin G, et al. T1 and T2* relaxation time in the parcellated myocardium of healthy Taiwanese participants: a single center study. Biomed J 2021;44:S132–43.
[50] Emer J. Platelet-rich plasma (PRP): current applications in dermatology. Skin Ther Lett 2019;24:1–6.
[51] Martínez-Martínez A, Ruiz-Santiago F, García-Espinosa J. Platelet-rich plasma: myth or reality? Radiologia 2018;60:465–75.
[52] Everts P, Onishi K, Jayaram P, Lana JF, Mautner K. Platelet-rich plasma: new performance understandings and therapeutic considerations in 2020. Int J Mol Sci 2020;21:7794.
[53] Kim DH, Lee MS, Lee S, Yoon SH, Shin JW, Choi SS. A prospective randomized comparison of the efficacy of ultrasound- vs fluoroscopy-guided genicular nerve block for chronic knee osteoarthritis. Pain Physician 2019;22:139–46.
[54] Chen JL, Chen CH, Cheng CH, Chen CC, Lin KY, Chen CPC. Can the addition of ultrasound-guided genicular nerve block using 5% dextrose water augment the effect of autologous platelet rich plasma in treating elderly patients with knee osteoarthritis? Biomed J 2021;44:S144–53.