Original Article: The diagnostic value of interleukin-6 in the degree of pulmonary destruction in patients with covid-19: a systematic review and meta-analysis

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ABSTRACT

Introduction: This is because the development of cytokine release syndrome (CRS) as the pathologic basis for the progression of severe Covid-19 disease is possible. **Material and Methods:** A two-step selection process that involved first screening studies based on their titles and abstracts and then reading the full texts of those studies was carried out independently by the two reviewers. Studies were considered if they were RCTs, observational cohorts, or case-control in design, described two or more patients diagnosed with Covid19, and reported measures of cytokine levels. The use of standardized data extraction tables allowed for the duplication of the data extraction process. Data were taken from the text of the article, the tables, and the graphs. **Results:** In all of the studies that were included, elevated IL-6 levels were found in Covid-19 patients. Numerous studies specifically found that patients with more severe diseases had higher levels of IL-6 descriptions of other inflammatory markers, such as ferritin and IL2R. Six studies in total compared the levels of IL-6 in patients with complicated disease and noncomplicated disease. **Conclusion:** In this systematic review and meta-analysis, we show that elevated serum IL-6 levels are associated with complicated Covid 19 disease and that these elevated IL-6 levels are also significantly associated with poor clinical outcomes. These results underline the necessity of continuing, carefully designed clinical studies to clarify the function of immunomodulation, specifically IL-6 inhibition, in the treatment of severe Covid-19.

Introduction

The The severe acute respiratory syndrome coronavirus 2 (SARS CoV2) first surfaced in Wuhan, China, in December 2019 [1-3]. This is the third zoonotic coronavirus to infect humans in the previous 20 years, causing the febrile respiratory illness coronavirus disease 2019 (Covid-19) [4-6]. With several million patients infected worldwide, SARS-CoV2 has

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proven to have a rapid capacity for dissemination in comparison to its predecessors. The high intrinsic reproductive number of 22.5 and the potential for occult transmission during the presymptomatic incubation period have all contributed to this transmission's growth in the community [7-9].

Nearly one-fifth of infected patients in China experience severe or critical illness, with a case fatality rate of 23% overall and up to 61% of patients experiencing severe complications. Host-directed therapeutics using already-available immunomodulatory agents must be investigated in addition to preventative vaccines and antiviral treatments. Acute respiratory distress syndrome (ARDS) may develop as a result of coronaviruses' ability to trigger excessive and unbalanced host immune responses. Autopsy examinations of patients with Covid-19 complicated by ARDS show hyperactivation of cytotoxic T cells with high concentrations of cytotoxic granules. According to studies describing the immunological profile of critically ill patients with Covid19, interleukin (IL)6 hyperproduction is a key mediator of respiratory failure, shock, and multiorgan dysfunction. Characterizing this dysregulation of host immune responses is crucial because it may serve as a target for therapeutics [10-12].

This is because the development of cytokine release syndrome (CRS) as the pathologic basis for the progression of severe Covid-19 disease is possible. As a result, we created a systematic review and meta-analysis to evaluate the evidence describing the IL-6 response in patients with Covid-19 in order to aid in patient diagnosis, define the immunogenic profile of Covid-19, and guide future trials aimed at this immune mediator [13-15].

Material and Methods

Design

We carried out a thorough analysis and meta-analysis to look into IL-6 dysregulation in Covid-19 patients. Articles that characterized serum IL6 dynamics in adult or pediatric patients with Covid-19 were eligible for inclusion. These articles could be observational cohort, case-control, or randomized controlled trials (RCTs). The Cochrane Handbook's guidelines for methodology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for reporting were followed when conducting this systematic review [16-18].

Search tactics

Our high sensitivity search strategy included clusters for Covid-19, IL-6, or tocilizumab, as well as free text and keyword search term synonyms (see Appendix S1 for a complete list of search strategies). Then, using Ovid MEDLINE, EMBASE, and Google Scholar, we conducted a methodical search for published articles. Further searches using the terms "tocilizumab" and "interleukin" were carried out in preprint servers (Biorxiv, Medrxiv, and Chinxiv) to find potential manuscripts for prepublication that met the requirements. From January 1 to March 15, 2020, these searches were conducted [19].

In order to ensure that all studies reporting data on IL6 levels in Covid-19 were found, we next performed a second, expanded Ovid MEDLINE and EMBASE database search from January 1, 2020, to March 15, 2020 for all published cohort studies reporting Covid–19 patient characteristics and outcomes only. Language, disease severity, or reported outcomes were not excluded in any way. Search results from Google Scholar and the preprint servers were manually parsed to find any eligible studies. Citations from MEDLINE and EMBASE were managed with Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) to make it easier to remove duplicates. All included articles' reference lists were examined for potential citation eligibility [20].

Data extraction and study selection

A two-step selection process that involved first screening studies based on their titles and abstracts and then reading the full texts of those studies was carried out independently by the two reviewers. Studies were considered if they were RCTs, observational cohorts, or case-control in design, described two or more patients diagnosed with Covid19, and reported measures of cytokine levels (with a focus on IL-6). The use of standardized data extraction tables allowed for the duplication of the data extraction process. Data were taken from the text of the article, the tables, and the graphs (using tools for figure analysis to quantitatively take data from curves) [21-23].

Data were gathered for the study's design and setting, patient demographics, disease characteristics, immune marker levels, indicators of systemic inflammation (inflammatory markers and cytokine levels), immunomodulatory drugs used (corticosteroids or intravenous immunoglobulin [IVIg]), and outcomes consistent with complicated infection (hospitalization, intensive care unit (ICU) admission, ARDS, invasive mechanical ventilation, renal replacement therapy, and severe infection) [24-26].

Statistical investigation

Continuous data is presented as means and standard deviations (SDs), or medians and interquartile ranges (IQR), or range, while count data and nominal variables are presented as proportions with percentages. As data availability allowed, both unadjusted and adjusted versions of the measures of association relating clinical characteristics or IL-6 levels with downstream clinical outcomes are presented. Results are described and summarized quantitatively and semi-qualitatively; random effects models were used in a meta-analysis for data that were deemed sufficiently homogeneous in terms of patient characteristics, interventions, and clinical outcomes [27-29].

To increase the number of studies eligible for meta-analysis, medians and IQRs were converted to means with SDs for statistical homogeneity. We calculated the ratio of means (RoM) for each study and then performed a meta-analysis using general inverse variance methods (DerSimonian and Laird) to generate pooled measures of association, corresponding 95 percent confidence intervals (95 %CI), and forest plots. Individual sub-definitions of complicated disease (as determined by the primary study investigators) were the subject of prespecified subgroup analyses. All statistical tests and confidence intervals had a predetermined alpha of .05, and the I 2 statistic was used to determine the degree of statistical heterogeneity. Microsoft Excel version 16 and Review Manager version 5 were both used for the data analysis [30-32].

Risk of bias

All included studies were evaluated for bias risk by two reviewers in separate reviews. For cohort studies linking IL-6 levels with disease severity, the updated Quality in Prognostic Studies (QUIPS) tool was used [33].

Results

After eliminating duplicates, our database search found 1219 distinct citations. Of these, 112 articles were evaluated via full text, and eight studies were qualified for inclusion. Two additional articles were found through searches on preprint servers. Thus, a total of 10 articles were qualified for inclusion, of which 10 contributed to the qualitative synthesis and six to the quantitative synthesis (metaanalysis). The remaining four studies were also qualified for inclusion, but their data were not presented in a way that allowed for the computation of RoMs, so they were not combined in the meta-analysis.

After removing duplicates, our database search found 1219 distinct citations. Of these, 112 articles were evaluated via full text, and eight studies qualified for inclusion. Two additional articles were found through searches on preprint servers. There were thus a total of 10 articles that could be included, with 10 of them contributing to a qualitative synthesis and six of them undergoing a quantitative synthesis (metaanalysis). The final four studies were still eligible for inclusion, but they were excluded from the meta-analysis because they did not present their data in a way that allowed RoMs to be calculated.

In all of the studies that were included, elevated IL-6 levels were found in Covid-19 patients. Numerous studies specifically found that patients with more severe (complicated) diseases had higher levels of IL-6 descriptions of other inflammatory markers, such as ferritin and IL2R. Six studies in total compared the levels of IL-6 in patients with complicated disease (those with ARDS, needing ICU admission, or having "severe" or "critical" presentations according to the Chinese New Coronavirus Pneumonia Prevention and Control Program score) and noncomplicated disease (those without the aforementioned criteria present).

Statistical heterogeneity was elevated throughout all analyses, and it did not significantly decrease with the planned sensitivity analyses, which were restricted to studies comparing patients requiring ICU admission vs. no ICU admission. Patients with complicated Covid-19 had IL-6 levels that were 2.90 times higher than those with noncomplicated disease(Fig 1).

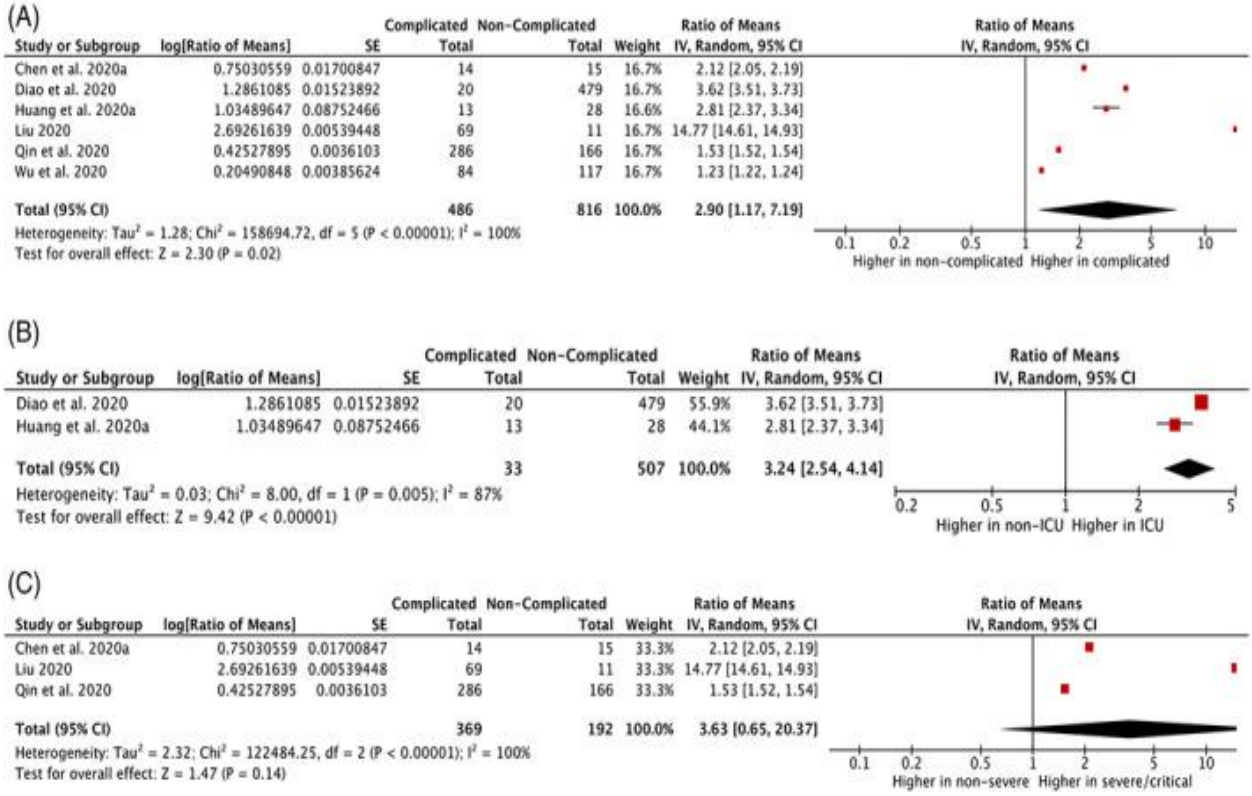

Figure 1: Meta-analysis result

In the retrospective cohort study by Liu et al. it is noteworthy that baseline IL-6 levels positively correlated with bilateral pulmonary involvement, maximum body temperature, and IL-6 assessment before and after treatment. Out of 30 patients with IL-6 assessment before and

after treatment, 26 (87 percent) patients had significantly lower IL-6 in line with improving pulmonary computed tomography. In contrast, three (or 75 percent) of the four patients who experienced progressively worsening clinical conditions had rising IL-6 levels.

According to Wu et al.'s analysis of risk factors for ARDS and death, patients with Covid-19 who developed ARDS had significantly elevated IL-6 levels. Elevated IL-6 was also linked to fatality.

In a similar vein, Ruan et al found that patients who succumb to Covid19 have significantly higher IL-6 levels than those who survive.

In cohort studies evaluating the inflammatory response in Covid19, the risk of bias was evaluated using the QUIPS tool. Inconsistencies in the measurement of the inflammatory mediators under investigation and a lack of confounding control were the main reasons for the designation of four studies as having a high risk of bias and five as having a moderate risk of bias(Fig 2).

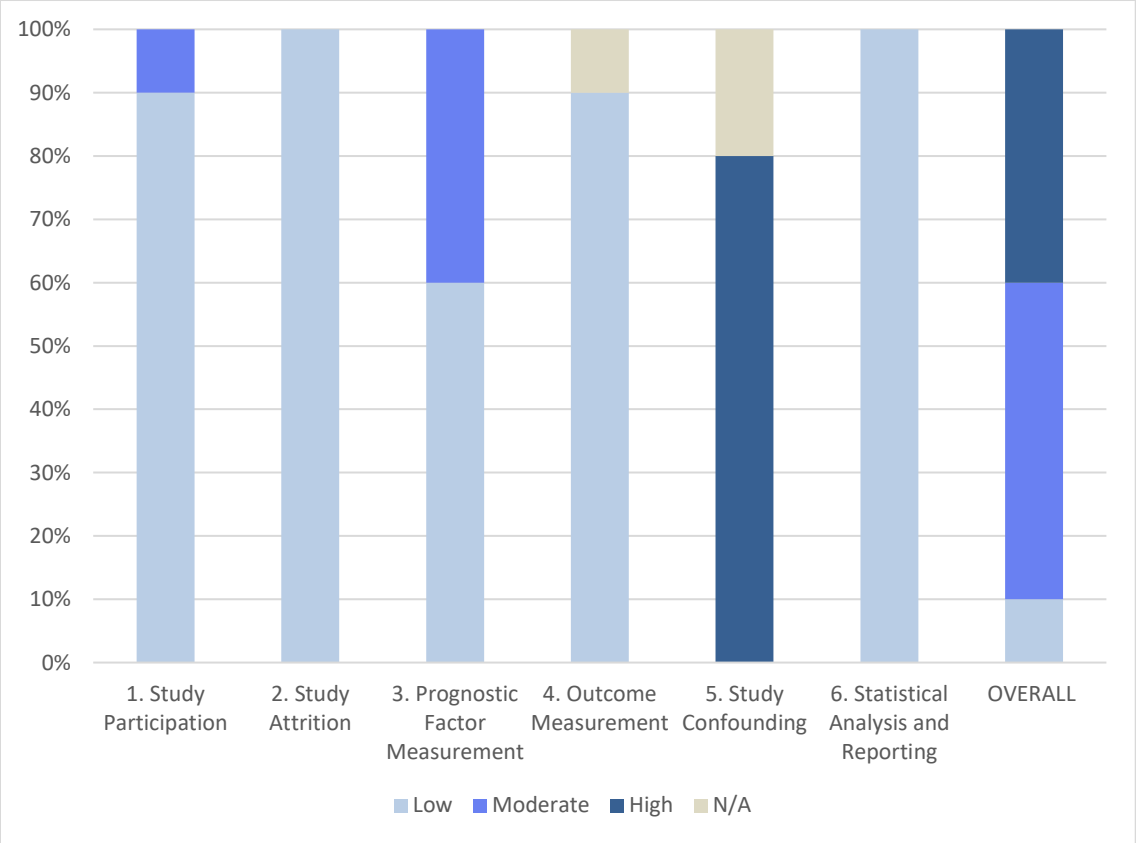

Figure 2: risk of bias results

Discussion

Coronaviruses are a group of single-strain RNA viruses that infect a variety of hosts, including people, and are primarily responsible for respiratory infections. A novel betacoronavirus called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused more than 1 point 9 million deaths and became a global pandemic at the end of 2019, first appeared in China. It has since infected nearly 90 million people worldwide [33].

Acute bilateral pneumonia, which can progress to acute respiratory distress syndrome and multi-organ failure, develops in 20% of patients even though the majority of cases only have mild symptoms. With age and the presence of comorbidities, the risk of a fatal illness rises. A counterproductive host immune response follows the first phase of SARS-CoV-2 infection,

which is characterized by a high level of viral replication(Fig 3) [34-36].

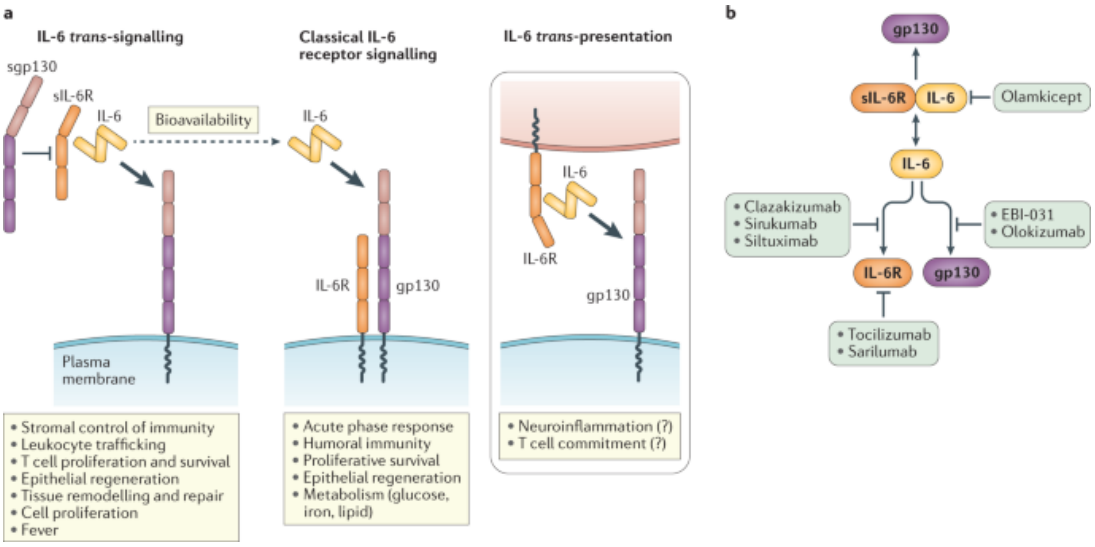

Figure 3: Mechanism of IL-6 In COVID-19

According to the severity and prognosis, this infection has been divided into three clinical stages. Stage I is characterized by mild, non-specific symptoms like myalgia, a dry cough, a headache, and a subfebrile temperature, but no other abnormalities in the lab or on imaging. Cough, high fever, dyspnea, abnormal thoracic imaging, lymphopenia, and elevated inflammatory marker levels are the hallmarks of stage II [37-39].

Depending on whether hypoxemia is present (IIb) or not (IIa), it is further divided into two groups. Stage III culminates in severe respiratory failure with a poor prognosis, showing clinical signs of a severe systemic inflammatory syndrome. Several inflammatory markers have extremely high values during this stage of the illness, and macrophage activation syndrome may occur.

The various COVID-19 treatments that have been tried can be categorized into three main groups: medications with a direct antiviral effect, medications with an immunomodulatory effect, and neutralizing antibodies from convalescent plasma. Remdesivir has so far been regarded as the most important medication for the first group because it has been shown to have a quicker clinical improvement and a lower mortality rate in the subset of hospitalized patients who are receiving oxygen. There are still questions about the treatment's effectiveness and the types of patients who might benefit the most from this therapeutic, though, as these data conflict with those from other studies [40].

A therapeutic approach called immunomodulation has been promoted in light of the difficulty in preventing the spread of viruses and the lack of a treatment that is unquestionably effective against them. This tactic is especially pertinent in light of the high levels of proinflammatory cytokines that are known to play a key role in the pathophysiology of severe COVID-19 (14). In these circumstances, the immune response loses its capacity to provide negative feedback, which results in an overproduction of inflammatory cytokines, harmful effects, and a poor prognosis. IFN-gamma, granulocyte colony-stimulating factor (G-CSF) [41-43], granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein 1 (MIP-1alpha/CCL3) [44-46], monocyte chemoattractant protein-1 (MCP-1/CCL2), and

interleukin-1 (IL-1) [47], among many others, have all been identified as significantly increased in severe COVID-19 patients. The fact that some of them, including IL-6, IL-8, and TNF-, are considered independent markers of the severe disease (19) is crucial [48].

For a better comprehension of the pathological process in COVID-19 and consequently for the identification of the most suitable therapeutic targets and timing of drug administration, a deeper understanding of the SARS-CoV-2-induced cytokine storm, including its triggering mechanisms, molecular components, and kinetics, is required. So far, several studies have been published on the potential effects of both specific (anti-IL-6, anti-IL-1, anti-GM-CSF, and anti-TNF-) and non-specific (corticosteroids) immunomodulatory therapies for COVID-19.

Corticosteroids, particularly dexamethasone, have been the most widely used, especially in light of growing evidence of their benefit in reducing mortality in hospitalized patients receiving oxygen and particularly in patients supported by mechanical ventilati [49]. The best dosage for each patient, the precise timing of administration, and the length of the course of treatment still need to be clarified. Additionally, a more focused medication would be preferable, especially in light of the current immune dysfunction.

In this systematic review and meta-analysis, we show that severe Covid 19 disease is associated with significantly elevated serum levels of IL-6.

According to a meta-analysis of the data, these elevated levels are strongly linked to poor clinical outcomes, such as ICU admission, ARDS, and death. When compared to patients with non-complicated disease, those with such complicated forms of Covid-19 had serum IL-6 levels that were nearly three times higher.

It is becoming more widely accepted that a dysregulated host immune response to foreign infectious pathogens is essential to the development of target organ dysfunction and a significant cause of morbidity and mortality. The systemic inflammatory response in sepsis has been shown to be similar to that of CRS; consequently, in patients with Covid-19 complicated by ARDS, such hyperactivation of the humoral immune system with a prominent IL-6 response may imply that part of the pathogenesis of complicated disease involves a dysregulated and excessive host inflammatory response.

This clinical phenotype resembles that of CRS, a condition for which tocilizumab's IL-6 receptor inhibition has demonstrably shown benefit, and it may indicate a Covid-19 subpopulation that is more severely affected, requiring more intensive care and having worse clinical outcomes. Studies evaluating the potential benefit of host-directed immunomodulatory therapy are desperately needed because there is a chance that CRS could develop as the pathologic basis for a severe Covid-19 infection.

Inhibiting IL-6 with siltuximab, sariliumab, and tocilizumab is one of many clinical trials looking at the potential use of biologic inhibitors of important cytokine pathways as a treatment for complicated Covid-19 [50]. While the results of these randomized trials are eagerly awaited, early clinical studies of tocilizumab and siltuximab in severe Covid-19 are encouraging, showing signs of potential for clinical and radiographic improvement.

Conclusion

In this systematic review and meta-analysis, we show that elevated serum IL-6 levels are associated with complicated Covid 19 disease and that these elevated IL-6 levels are also significantly associated with poor clinical outcomes. This implies that an excessive host immune response and autoimmune injury may be the result of an initial SARS-CoV2 infection that progresses to a complicated disease. These results underline the necessity of continuing, carefully designed clinical studies to clarify the

function of immunomodulation, specifically IL-6 inhibition, in the treatment of severe Covid-19.

References

[1] R. Azhough et al., Pilonidal sinus surgery with mechanical drilling technique. Indian Journal of Surgery. **2020**;82:824-7. [Crossref], [Google Scholar], [Publisher]

[2] N. Forghani, et al., Fulminant Guillain-Barre syndrome associated with SARS-CoV-2: A case series. J Clin Images Med Case Rep. **2022**;3(1):1626. [Crossref], [Google Scholar], [Publisher]

[3] K. Shahsavarinia, et al., Diagnostic value of red blood cell distribution width in patients with organophosphate poisoning in emergency department of Sina hospital in 2019. J Clin Images Med Case Rep. **2022**;3(2):1634. [Crossref], [Google Scholar], [Publisher]

[4] S. Eskandari, et al., Relationship between patent foramen ovale and COVID-19 in patients admitted to an intensive care unit. Revista Espanola De Cardiologia (English Ed). **2021**;74(8):725. [Crossref], [Google Scholar], [Publisher]

[5] P. Jalali, et al., GUCA2A Dysregulation as a Promising Biomarker for Accurate Diagnosis and Prognosis of Colorectal Cancer. **2023**. [Crossref], [Google Scholar], [Publisher]

[6] SM. Haghdoost, MK. Gol, The necessity of paying more attention to the neurological and psychological problems caused by the COVID-19 pandemic during pregnancy. Health. **2020**;3(4). [Crossref], [Google Scholar], [Publisher]

[7] MK. Gol, D. Aghamohamadi., Effect of massage therapy with and without elastic bandaging on pain, edema, and shoulder dysfunction after modified radical mastectomy: a clinical trial. International Journal of Women's Health and Reproduction Sciences. **2020**;8(1):73-8. [Crossref], [Google Scholar], [Publisher]

[8] MK. Gol, et al., Design and psychometrics cultural competence questionnaire for health promotion of Iranian nurses. Journal of education and health promotion. **2019**;8. [Crossref], [Google Scholar], [Publisher]

[9] K. Hashemzadeh, et al., Effects of Foot Reflexology on Post-sternotomy Hemodynamic Status and Pain in Patients Undergoing Coronary Artery Bypass Graft: A Randomized Clinical Trial. Crescent Journal of Medical & Biological Sciences. **2019**;6(4). [Google Scholar], [Publisher]

[10] M. Khanbabayi Gol, et al., Frequency ratio of carpal tunnel syndrome in women with breast cancer treated with lymphedema in Tabriz medical education centers; 2018-2019. The Iranian Journal of Obstetrics, Gynecology and Infertility. **2020**;22(12):62-8. [Crossref], [Google Scholar], [Publisher]

[11] L.H Anvar, et al., The study of rs324420 (C385A) polymorphism of the FAAH gene of the endocannabinoid system in patients with epilepsy and ADHD. Epilepsy Research, **2023**. 192: p. 107100. [Crossref], [Google Scholar], [Publisher]

[12] A. Mobed, et al., Biosensors technology for anti-epileptic drugs. Clinica Chimica Acta, **2022**. 533: p. 175-182. [Crossref], [Google Scholar], [Publisher]

[13] S. Charsouei, S., et al., Evaluation of Three- and Five-Year Disease-Free Survival in Patients With Cervical Cancer With Spinal Cord Metastasis Under Treatment With External Radiotherapy+ Brachytherapy. International Journal of Women's Health & Reproduction Sciences, **2022**. 10(2). [Google Scholar], [Publisher]

[14] M. Zamani Esfahlani, et al., Oral Levothyroxine Prophylactic Administration on Bleeding and Hemoglobin Changes During and after Total Hip Arthroplasty in Patients with a History of Ischemic Heart Disease: A Randomized Clinical Trial. Trauma Monthly,

2023. 28(3): p. 805-814. [Google Scholar], [Publisher]
[15] K. Komlakh, et al., Designing a Guideline for Elective and Emergency Spinal Cord Surgeries During the COVID-19 Pandemic. Trauma Monthly, **2022**. 27(Especial Issue (COVID-19 and Emergency Medicine)): p. 1-7. [Crossref], [Google Scholar], [Publisher]
[16] S. Charsouei, et al., Effects of COVID-19 pandemic on perceived stress, quality of life, and coping strategies of women with breast cancer with spinal metastasis under chemotherapy. Int. J. Women's Health Reprod. Sci, **2021**: p. 55-60. [Crossref], [Google Scholar], [Publisher]
[17] S.M. Haghdoost, and M.K. Gol, The necessity of paying more attention to the neurological and psychological problems caused by the COVID-19 pandemic during pregnancy. Health, **2020**. 3(4). [Crossref], [Google Scholar], [Publisher]
[18] M.K. Gol, and D. Aghamohamadi, Effect of massage therapy with and without elastic bandaging on pain, edema, and shoulder dysfunction after modified radical mastectomy: a clinical trial. International Journal of Women's Health and Reproduction Sciences, **2020**. 8(1): p. 73-8. [Crossref], [Google Scholar], [Publisher]
[19] M.K. Gol, A. Dorosti, and M. Montazer, Design and psychometrics cultural competence questionnaire for health promotion of Iranian nurses. Journal of education and health promotion, **2019**. 8. [Crossref], [Google Scholar], [Publisher]
[20] K. Hashemzadeh, M. Dehdilani, and M.K. Gol, Effects of Foot Reflexology on Post-sternotomy Hemodynamic Status and Pain in Patients Undergoing Coronary Artery Bypass Graft: A Randomized Clinical Trial. Crescent Journal of Medical & Biological Sciences, **2019**. 6(4). [Google Scholar], [Publisher]
[21] M. Khanbabayi Gol, M. Eidy, and M. Zamani Esfahlani, Frequency ratio of carpal tunnel syndrome in women with breast cancer treated with lymphedema in Tabriz medical education centers; 2018-2019. The Iranian Journal of Obstetrics, Gynecology and Infertility, **2020**. 22(12): p. 62-68. [Crossref], [Google Scholar], [Publisher]
[22] N. Shahidi, F. Mahdavi, and M.K. Gol, Comparison of emotional intelligence, body image, and quality of life between rhinoplasty candidates and control group. Journal of Education and Health Promotion, **2020**. 9. [Crossref], [Google Scholar], [Publisher]
[23] S. Jiang, et al., A meta-analysis review of the effect of Zn-doped synthetic polymer materials on bone regeneration. Journal of Drug Delivery Science and Technology, **2022**: p. 103792. [Crossref], [Google Scholar], [Publisher]
[24] V Tajiknia, S Hassani, H Seifmanesh, A Afrasiabi, H Hosseinpour, J. Obstetrics Gynecology and Reproductive Sciences, **2021** 5 (9) [Crossref], [Google Scholar], [Publisher]
[25] SM Shushtarian, M Reza soltani, MJ Namazi, Journal of Advanced pharmacy Education& Research. **2020**;10:(s2) [Google Scholar], [Publisher]
[26] SM Bagheri, S Hassani, A Salmanipour, GSC Advanced Research and Reviews, **2022** 11 (3), 101-105 [Crossref], [Google Scholar], [Publisher]
[27] SH AH Maleki,A Gholami, M Mohammadi, A Farhiudian, Journal of pharmaceutical Negative Results, **2022** 13 (10), 4137-4158 [Crossref], [Google Scholar], [Publisher]
[28] SAY Ahmadi; et al, Formerly Current Pharmacogenomics Journal.**2020**, 17(3): 197-205 [Crossref], [Google Scholar], [Publisher]
[29] SAK AH Jalali, AH Maleki, S Hassani, E Khoshdel, The seybold Report Journal, **2023** 18 (05), 999-1022 [Google Scholar], [Publisher]
[30] S Sayad; et al, Archive of Oncology Journal.**2020** ;26(1): 6-9 [Crossref], [Google Scholar], [Publisher]

[31] S Sayad; et al, Annals of Research in Antioxidants Journal.**2019**; 4(2) [Crossref], [Google Scholar], [Publisher]
[32] S Moshar, MR Soltani, MJ Namazi, Journal of Advanced pharmacy Education & Research.**2020**; 10:(s2) [Google Scholar], [Publisher]
[33] S Hassani, M Rikhtehgar, A Salmanipour, GSC Biological and Pharmaceutical Sciences, **2022** 19 (3), 248-252 [Crossref], [Google Scholar], [Publisher]
[34] S Habibollahi Khaled hamid,M Eghbalnejad Mofrad, SMA Alavi, MJ Namazi, Journal of Advanced pharmacy Education & Research. **2021**;10 185-187 [Google Scholar], [Publisher]
[35] MR AH Jalali, S Hassani, S Albuzyad, A Moaddab, The seybold Report Journal, **2023** [Google Scholar], [Publisher]
[36] M.E Akbari; et al, International Journal of Cancer Management.2016;9(6) [Crossref], [Google Scholar], [Publisher]
[37] FB AH Jalali,S Hassani, A Zare,T Ziaadini, The seybold Report Journal, **2023** 18 (04), 1634-1653 [Google Scholar], [Publisher]
[38] F Safari, H Safari, Eurasian Journal of Chemical, Medicinal and Petroleum Research, **2022** 1 (2), 150-154 [Google Scholar], [Publisher]
[39] F Rokhtabnak, S Sayad, M Izadi, SD Motlagh, P Rahimzadeh, Anesthesiology and Pain Medicinem **2021** 11 (5) [Crossref], [Google Scholar], [Publisher]
[40] F HYSENI; et al, The Importance of Magnetic Resonance in Detection of Cortical Dysplasia, Curr Health Sci Journal. **2021**; 47(4): 585–589 [Crossref], [Google Scholar], [Publisher]
[41] F Beiranvandi, Z Kuchaki, A Zare, E Khoshdel, A Jalali, Journal of Pharmaceutical Negative Results, **2022**, 4417-4425 [Crossref], [Google Scholar], [Publisher]
[42] E. Ghaibi, et al., Eurasian Journal of Chemical, Medicinal and Petroleum Research, **2022**, 1, 33-39. [Google Scholar], [Publisher],
[43] E Harizi; et al, Radiology Case Reports **2022** 17 (11) 4152-4155 [Crossref], [Google Scholar], [Publisher]
[44] E Kola, A Gjata, I Kola, et al., Radiology Case Reports, **2022** 17 (3), 1032 [Crossref], [Google Scholar], [Publisher]
[45] E Kola, A Gjata, I Kola, A Guy, J Musa, et al., Radiology Case Reports, **2021** 16 (11), 3191-3195 [Crossref], [Google Scholar], [Publisher]
[46] E Ghasemi, AH Fathi, S Parvizinia., J Iran Dent Assoc **2019**; 31 (3):169-176 [Crossref], [Google Scholar], [Publisher]
[47] D Nakuci, E Kola, E Horjeti, I Kola, B Shaipi, J Musa, A Guy, M Alimehmeti, Archives of Clinical and Medical Case Reports, **2020** 4 (5), 760-765 [Google Scholar], [Publisher]
[48] D Nakuci, E Kola, E Horjeti, I Kola, B Shaipi, J Musa, A Guy, M Alimehmeti, Archives of Clinical and Medical Case Reports, **2020** 4 (5), 760-765 [Google Scholar], [Publisher]
[49] A. Mobed et al., Biosensors technology for anti-epileptic drugs. Clinica Chimica Acta. **2022**;533:175-82. [Crossref], [Google Scholar], [Publisher]
[50] A Jalali, S Hassani, S Albuzyad, A Moaddab, M Rajabzadeh, Pakistan Heart Journal, **2023** 56 (2), 906-919 [Google Scholar], [Publisher]