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KUWAIT MEDICAL JOURNAL
The Official Journal of The Kuwait Medical Association

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KU ISSN 0023-5776

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Vol. 56 No. 4 DECEMBER 2024

KUWAIT MEDICAL JOURNAL

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PUBLISHER: The Kuwait Medical Journal (KU ISSN-0023-5776) is a quarterly publication of THE KUWAIT MEDICAL ASSOCIATION. Address: P.O. Box 1202, 13003 Safat, State of Kuwait; Telephone: 1881181 Fax: 25317972, 25333276. E-mail : kmj@kma.org.kw

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Kuwait Medical Journal

Published by the Kuwait Medical Association
Previously known as The Journal of the Kuwait Medical Association (Est. 1967)

EDITORIAL ADDRESS

P.O. Box: 1202, 13003-Safat, Kuwait
Telephone: (00-965) 1881181(Ext. 114, 115) - Fax: (00-965) 25317972, 25333276
E-mail: kmj@kma.org.kw
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Article: Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, ***et al***. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

Book: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

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Review Article

Prevalence and consequential outcomes of concurrent infections involving both SARS-CoV-2 and influenza viruses

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Kuwait Medical Journal 2024; 56 (4): 284 - 300

ABSTRACT

This review article focuses on some of the complex interplays and public health implications of co-infection caused by both SARS-CoV-2 and influenza viruses. The geographic distribution for such co-infections was highly diverse throughout the world; however, this posed formidable impediments for the clinical and public health sectors, mainly due to the symptomatologic and mode of transmission overlap of these viruses. This article critically looks at the data collected in the years 2020 through to 2024 and has selected rigorously the methodologies used to pick relevant studies. The present findings underline the enhanced severity of clinical outcomes in co-infected patients, which includes higher ICU admissions, ventilator support and morality, compared with patients infected by each virus alone. The paper will be an eye-opener for effective surveillance systems, accurate diagnostic tools and comprehensive vaccine strategies in the management of the impacts of these co-infections. The study also recommended that the real prevalence of the coinfections is likely underreported due to diagnostic challenges, hence the need to develop test methods that will be able to diagnose the viruses fast and accurately. In summary, co-infection of COVID-19 with influenza presents a compounded public health challenge, with the already outnumbered capacities and cohesive responses toward mitigation risks associated with these concurrent infections. In addition, insights seek to inform future strategies in preparedness for vaccines and healthcare approaches taking an integrated route aimed at the dual threat posed by these prevailing respiratory viruses.

KEY WORDS: coinfection, influenza virus, pathogenesis, SARS-CoV-2

INTRODUCTION

Since the beginning of COVID-19 in the last months of 2019, the global outbreak triggered by SARS-CoV-2 virus has risen into a significant global health catastrophe. COVID-19 pandemic, commencing from this SARS-CoV-2, spread with an overwhelming rate throughout regions, compelling persistent health care encounters and obligations on a multitude of populations[1]. As of June 7, 2023, the growing impact of COVID-19 pandemic was calculated at approximately 767.7 million confirmed cases and 6.9 million deaths globally, making it one of the utmost overwhelming health crises of the era[2]. The World Health Organization (WHO) declared the end of the emergency phase of the pandemic on May 5, 2023, suddenly, with a major consequence[3]. However, the end of the emergency status does not mean that the virus is eradicated. The ever-adapting and changing nature of SARS-CoV-2 through genetic mutations raises a possibility of an equilibrium state, suggesting

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its continuous coexistence with human hosts like infections by influenza viruses[4]. The real challenge, in other words, really underscores how important it is to keep an eye on these variants through research on viral mutation and perfecting our public health adaptive approaches for outbreaks to come. SARS-CoV-2 is a persistent event that emphasizes worldwide health attentiveness in the front of developing infectious diseases and the requirement for international collaboration in the progress of vaccine development, surveillance and response mechanisms to protect public health[5].

The simultaneous occurrence of COVID-19, caused by the prominent SARS-CoV-2 virus, and influenza in the population significantly disrupted the efforts of healthcare authorities[6]. In 2017, the flu had a significant impact, causing hospitalization for between 3 to 22 million individuals and resulting in the death of around 99,000 to 200,000 persons globally[7]. The numerical values exhibit significant fluctuations, so illustrating the inherent variability of influenza throughout different years[8]. During the first stages of COVID-19 transmission, governments and communities implemented stringent measures like mandatory mask use, social distancing and complete lockdowns. Moreover, it is worth noting that not only did these steps reduce the spread of COVID-19, but they also slowed the spread of the flu[9]. Given the comparable modes of transmission, namely airborne transmission and contact with contaminated surfaces, implementing measures to mitigate the spread of both pathogenic viruses was effective in addressing both simultaneously[10]. Upon the relaxation of these preventive efforts, the influenza virus started a resurgence, indicating a plausible risk for a co-pandemic situation, whereby both viruses are concurrently spreading[11]. This situation entails the simultaneous presence of both viruses in the population, which greatly complicates the identification, prevention and treatment methods owing to their similar symptoms and spreading mechanisms. These are such complicated challenges to the clinical and public health sectors through the co-infection of one individual with SARS-CoV-2 and influenza virus, especially if they entered the body at the same time[12]. Such co-infections complicate the process not only for the patients to have proper diagnoses, but also give the possibility for co-infections to develop severe respiratory complications, which may lead to higher rates of the disease and death[13]. Experts now note that increased alertness in the surveillance of these viruses and issuance of comprehensive vaccines that can treat both is very important. Equally important is paying strict attention to the public health guidelines given on these respiratory diseases[14]. This further highlights the urgent need for a comprehensive approach to mitigating the effects of both seasonal flu and COVID-19, especially with new SARS-CoV-2 variants and challenges that come with co-infections[15]. The research is ongoing in this regard to increase vaccine efficacy, be well versatile with the virus-transmission dynamics, and be able to intervene with effective therapeutics[16].

HISTORY

The scientific studies strongly reiterate that there is a need for an all-encompassing strategy with respect to respiratory virus surveillance: not only for improvements in molecular diagnosis but also for epidemiological tracking and use with vaccinations as an appropriate mechanism in effecting control from the concomitant threats of COVID-19 along with influenza[16]. Greater focus on the status and prognosis of coinfection may lead to significantly furthering development in methodologies of prevention and treatment of the disease[17]. On the other side, literature available before the emergence of the COVID-19 pandemic indicated that, at large, 10% of infections due to the respiratory viruses showed simultaneous infections with the influenza virus[18]. This further demonstrates the complexity of viral interactions that might with as much relevance yield a deep impact on the transmissibility and pathogenic effect of infectious diseases, or foil vaccination campaigns[19]. Most of the research efforts implemented around the coinfections point out to the fact that patients suffering from coinfections are highly affected by the diseases, especially the elderly and those predisposed by underlying medical conditions, leading to exacerbated disease severities[20]. Gaining knowledge about the frequency of coinfection and the particular virus species will aid healthcare workers in implementing measures to prevent infection for monitoring viral infections and aid doctors in determining the most suitable antiviral treatment for individuals[21]. Furthermore, it is crucial to possess information about potential risk factors for coinfection and clinical results to evaluate the prognosis for patients[22]. In this context, it would be of high importance to know the real situation of this coinfection in detail, for any possible control measure[16,23]. This is crucial in the optimization of the surveillance systems of infectious diseases, which is key in the early identification and spread prevention of outbreaks. Further, the clarification of coinfection dynamics would be valuable to public health in devising tailor-made responses in the shifting landscape of viral pathogens[24]. The identification of

possible risk factors associated with coinfection and its clinical outcomes can have several implications from a clinical point of view, enabling better prognosis of the patients[25]. Comprehensive patient care does include verdict use of antiviral drug therapies thoughtfully, based on the specific viral co-pathogens present[26]. This leads to detailed studies of molecular interplay among co-infecting viruses, and their synergy for modulation of host physiology will be of immense importance in designing precise therapeutic interventions[27].

In fact, studies suggested that this genetic variation of a viral pathogen has some important implications for disease severity or treatment response when integrated with bioinformatic tools in genomics. Such technological improvements aid in the identification of new viral strains and the assessment of their pathogenicity; they may also provide some aid in identifying and appraising the potential of coinfections in causing diseases[28-30]. Multidisciplinary approach that is, merging epidemiological surveillance with molecular biology and clinical research is the only assurance of ensuring proper management of coinfections and improved outcome of patient care in this era of rapidly progressing and emerging infectious diseases[31]. The progression of the COVID-19 pandemic was complicated throughout with coinfections involving influenza, which noted varied substantial prevalence. It may, therefore, be correct to attribute these differences to the various parameters used in conducting the studies, among them the varying sample sizes, changing demographics of the study populations, and geographical as well as temporal aspects of the studies conducted[32]. This variety creates complexity in the understanding scope of the coinfection rates across the world. Without concise data, it may be quite difficult to make any conclusions regarding the effect of coinfection with COVID-19 and coinfection with influenza on clinical outcomes, including severity of symptoms and admission to intensive care units, mechanical ventilation and death rates[33,34].

This area of COVID-19 coinfection dynamics adds to an already huge scope of pathogens that have been deeply probed in existing literature[35]. However, this gap of specialized, detailed analyses explicitly dealing with coinfections that contain influenza underscores not only an area of very great need for careful investigation but also clearly points to a standing challenge for any such investigation[36]. Our review aims to fill this gap with robust assessment for the prevalence of coinfections, delineation of associated risk factors, and evaluation of consequential clinical impacts. The main aim is to add to increased understanding of how these coinfections may influence patient outcomes and inform strategies from health care that may mitigate adverse effects caused by concurrent infections. This will be critical in informing public health and clinical interventions aiming to mitigate COVID-19 and other co-circulating viral threats as the viruses continue to change and present new challenges.

LITERATURE REVIEW

We searched for the existing reviewed literature based on co-infection of influenza in patients with COVID-19 from 2020 to 2024 from such available databases as PubMed, Web of Science, the Cochrane Library, EMBASE, CNKI, among many others, based on a specified set of key terms, as shown in Table 1. At the same time, manual searching through the bibliographies of all relevant systematic reviews was done, making sure that we had not missed any studies and that we simultaneously searched for unpublished work on several preprint platforms. A PRISMA flow chart illustrates the steps to search for literature. The search yielded 770 articles. There were 470 articles chosen for further evaluation after removing duplicate papers; ultimately, 180 research papers were included in our study shown in Figure 1.

Evaluation standards

To define the scope of literature eligible for inclusion, we adopted the PICOs framework. The case definition referred to people who have confirmed COVID-19, as by the WHO through methods of diagnosis such as antigen rapid detection test or the nucleic acid amplification test, inclusive of the reverse transcription-polymerase chain reaction (RT-PCR). We considered individuals across all age demographics and at any stage of COVID-19 infection. Additionally, we defined the testing for co-infection of influenza and SARS-CoV-2 within 48 hours of any accepted testing modality's confirmed COVID-19 diagnosis (e.g., PCR or serology). The following study designs were considered acceptable: cross-sectional studies, cohort studies, case-control studies, randomized controlled trials and case series. The cross-sectional studies considered will include those in which the co-infection cases were detected in not less than 10 of the study sample sizes. Excluded in the literature types were conference abstracts, case reports and those involving animal subjects.

Extraction and evaluation of data

In the first phase, the screening of abstracts and titles was performed by two reviewers, Asif Mahmood, and Shama, to identify studies potentially suitable according to the inclusion criteria. The evaluators further checked the full text of the eligible studies they

Table 1: The proportion of co-infections among COVID-19 and influenza patients across various studies, including their 95% confidence intervals.

Author (Year)	Proportion of Co-infections	CI Lower Bound	CI Upper Bound	Number of Co-infections
Alpaydin (2020) [83]	0.0000	0.0000	0.1015	0
Babiker (2020) [84]	0.0000	0.0000	0.0787	0
Blasco (2020) [85]	0.0097	0.0017	0.0530	1
Brendish (2020) [86]	0.0000	0.0000	0.0191	0
Wang G (2020) [87]	0.5531	0.4938	0.6109	151
Yue (2020) [88]	0.5733	0.5174	0.6274	176
Yu (2020) [89]	0.1176	0.0932	0.1474	64
Burrel (2020) [90]	0.0166	0.0071	0.0383	5
Calderaro (2020) [91]	0.0000	0.0000	0.0448	0
Castillo (2020) [92]	0.0370	0.0066	0.1828	1
Chen N (2020) [93]	0.0000	0.0000	0.0374	0
Danis (2020) [94]	0.0769	0.0137	0.3331	1
DeSouza Luna (2020) [95]	0.0087	0.0015	0.0476	1
Hazra (2020) [96]	0.0065	0.0022	0.0190	3
Hughes (2020) [97]	0.0000	0.0000	0.0151	0
Kim D (2020) [98]	0.0086	0.0015	0.0472	1
Leuzinger (2020) [99]	0.0135	0.0037	0.0479	2
Lin (2020) [100]	0.0000	0.0000	0.0401	0
Ma (2020) [101]	0.4842	0.3863	0.5833	46
Massey (2020) [102]	0.0000	0.0000	0.0023	0
Matos (2020) [103]	0.0000	0.0000	0.1170	0
Nowak (2020) [104]	0.0008	0.0001	0.0047	1
Pongpirul (2020) [105]	0.0909	0.0162	0.3774	1
Richardson (2020) [106]	0.0005	0.0001	0.0028	1
Shah S (2020) [107]	0.0000	0.0000	0.1246	0
Si (2020) [108]	0.0000	0.0000	0.1380	0
Wang M (2020) [109]	0.0288	0.0099	0.0814	3
Wei (2020) [110]	0.2791	0.1675	0.4269	12
Wu C (2020) [111]	0.0058	0.0010	0.0320	1
Xing (2020) [112]	0.3529	0.2500	0.4716	24
Zhu (2020) [113]	0.0272	0.0133	0.0551	7
Liang (2020) [114]	0.0769	0.0137	0.3331	1
Chang (2020) [115]	0.1200	0.0944	0.1514	60
Wu P (2020) [116]	0.5238	0.4975	0.5500	726
Takahashi (2020) [117]	0.0033	0.0011	0.0095	3
Zhang C (2020) [118]	0.2647	0.1460	0.4312	9
Agarwal (2021) [119]	0.0891	0.0476	0.1607	9
Allou (2021) [120]	0.0323	0.0057	0.1619	1
Alosaimi (2021) [121]	0.3750	0.2522	0.5164	18
Chen S (2021) [122]	0.0115	0.0045	0.0292	4
Chung (2021) [123]	0.0000	0.0000	0.0653	0
DeClercq (2021) [124]	0.0000	0.0000	0.0897	0
Eisen (2021) [125]	0.0144	0.0066	0.0310	6
Freeman (2021) [126]	0.0000	0.0000	0.0132	0
Jongbloed (2021) [127]	0.0000	0.0000	0.0125	0
Cheng (2021) [128]	0.4554	0.3899	0.5225	97
Hashemi (2021) [129]	0.2190	0.1506	0.3073	23
Stowe (2021) [130]	0.0129	0.0100	0.0166	58
Kim KW (2021) [131]	0.0217	0.0060	0.0758	2
Kim Z (2021) [132]	0.0081	0.0014	0.0446	1
Kiymet (2021) [133]	0.0000	0.0000	0.0305	0
Li (2021) [134]	0.0370	0.0127	0.1033	3
Marshall (2021) [135]	0.0009	0.0002	0.0049	1
Masse (2021) [136]	0.0000	0.0000	0.0676	0
Mehta (2021) [137]	0.1200	0.0562	0.2380	6
Peci (2021) [138]	0.0000	0.0000	0.0117	0
Pigny (2021) [139]	0.0000	0.0000	0.0700	0
Rodriguez (2021) [140]	0.0192	0.0053	0.0674	2
Roh (2021) [141]	0.0088	0.0030	0.0255	3
Schneider (2021) [142]	0.0000	0.0000	0.1759	0
Singh (2021) [143]	0.0002	0.0000	0.0013	1
Sogaard (2021) [144]	0.0115	0.0020	0.0623	1
Tong (2021) [145]	0.5214	0.4392	0.6025	73
Liu (2021) [146]	0.0000	0.0000	0.0602	0
Zheng J (2021) [147]	0.1263	0.0927	0.1699	36
Scoot (2021) [148]	0.0000	0.0000	0.0051	0
Kawai (2021) [149]	0.0000	0.0000	0.0210	0
Ishiguro (2021) [150]	0.0940	0.0658	0.1324	28
Akhtar (2021) [151]	0.0172	0.0074	0.0397	5
Chekuri (2021) [152]	0.0000	0.0000	0.0124	0
Zhang G (2022) [153]	0.0769	0.0137	0.3331	1
Yilmaz (2022) [154]	0.0104	0.0018	0.0567	1
Trifonova (2022) [155]	0.0083	0.0023	0.0296	2
Tang (2022) [156]	0.3290	0.2877	0.3731	152
Sik (2022) [157]	0.0000	0.0000	0.2153	0
Shah M (2022) [158]	0.0013	0.0007	0.0023	12
Sapra (2022) [159]	0.0000	0.0000	0.0820	0
Rezaee (2022) [160]	0.0735	0.0641	0.0841	191
Ogunbayo (2022) [161]	0.0000	0.0000	0.0964	0
Kozinska (2022) [162]	0.0000	0.0000	0.0044	0
Kandeel (2022) [163]	0.0290	0.0080	0.0997	2
Eldesouki (2022) [164]	0.0159	0.0112	0.0226	30
Chen Y (2022) [165]	0.0000	0.0000	0.1936	0
Arguni (2022) [166]	0.3840	0.3034	0.4715	48
Alhoufie (2022) [167]	0.0307	0.0132	0.0698	5
Aggarwal (2022) [168]	0.0064	0.0027	0.0150	5
Swets (2022) [169]	0.0326	0.0287	0.0370	227
Suzuki (2023) [170]	0.0125	0.0090	0.0173	36
Steponaviciene (2023) [171]	0.0493	0.0379	0.0640	53
Milano (2023) [172]	0.0545	0.0187	0.1485	3
Lingani (2023) [173]	0.0031	0.0005	0.0173	1
Leong (2023) [174]	0.0051	0.0009	0.0280	1
Khasawneh (2023) [175]	0.1353	0.0874	0.2038	18
Fahim (2023) [176]	0.0092	0.0070	0.0120	52
Sulaiman (2023) [177]	0.0000	0.0000	0.0046	0
Owosu (2024) [178]	0.0766	0.0490	0.1178	18
Sabastin, (2024) [179]	0.0032	0.0009	0.0117	2
Çiçek Y (2024) [180]	0.0221	0.0165	0.0296	44
Sadeh Tehrani (2024) [181]	0.0129	0.0050	0.0326	4
Kandeel, A (2024) [182]	0.0026	0.0005	0.0146	1
Dietz, E (2024) [183]	0.0004	0.0002	0.0006	12
Ozaras, R (2024) [184]	0.0000	0.0000	0.0093	0
Martínez-Baz (2024) [185]	0.0093	0.0032	0.0269	3

felt were potentially suitable. This has been noted where possible, and Wen Zhang was asked to mediate and resolve the differences when the positions of the reviewers could not be reconciled. Asif Mahmood and Shama used pre-designed template forms to independently extract and assess the methodological quality of each study included in the review. The two reviewers shall resolve their disagreement through consensus. Should there be any lack of consensus between the reviewers, the issue was referred to the third reviewer for judgment. Details extracted from the article include the author, the year when the article was published, where the study was done, the period of the study and the design of the study. The demographics of the study population were to include gender, age and health status. The methodology of identifying SARS-CoV-2 and influenza co-infections, the number of COVID-19 patients tested for influenza, and the number of co-infections identified, along with

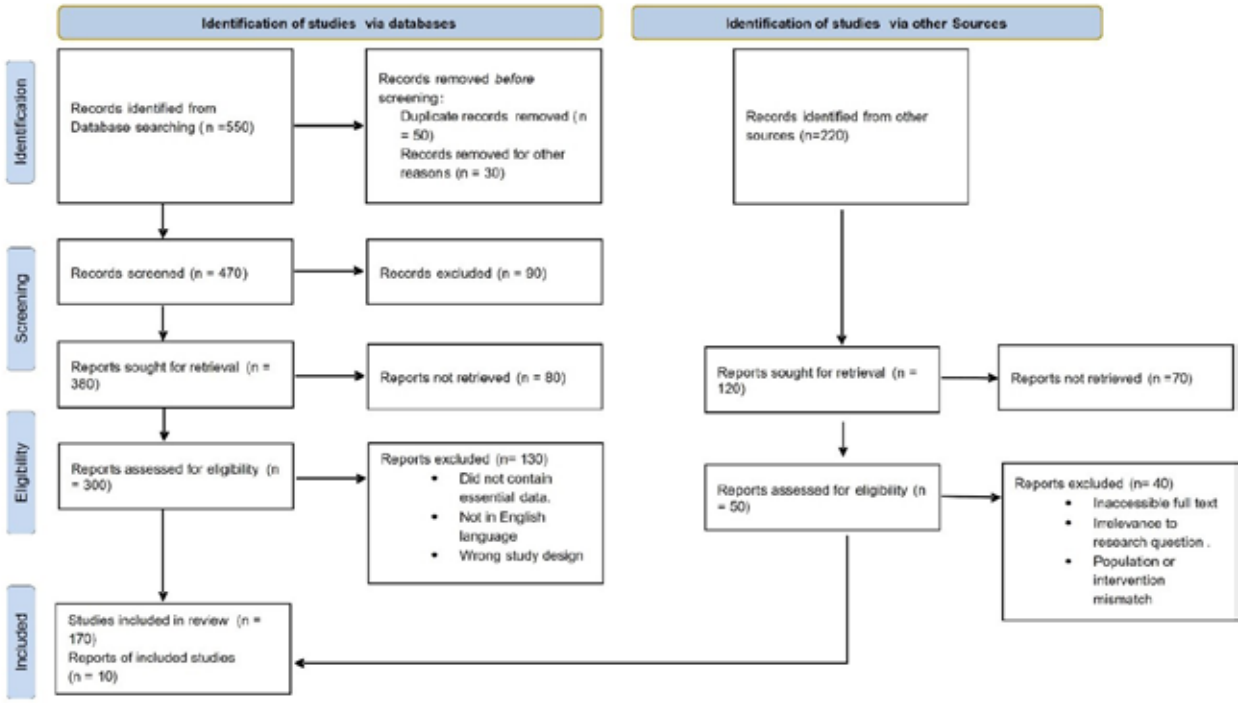

Figure 1: The PRISMA flow chart demonstrates the steps for conducting literature searches. A grand total of 770 items were identified. After removing duplicate articles, a total of 470 publications were chosen for additional study, finally leading to the inclusion of 180 studies for our study.

subtype distribution in the influenza virus, are reported. Specific details extracted included the outcomes observed in co-infection versus SARS-CoV-2 mono-infection cases, including symptoms, rates of intensive care unit admission, ventilator support and mortality.

Subsequent infections caused by SARS-CoV-2 and Influenza Viruses

Co-infections involving bacteria and viruses have historically been linked to worse outcomes during both pandemic and seasonal influenza. This basically strings delayed or missed diagnoses of concurrent COVID-19 and other respiratory infections[37,38]. With the appearance of the SARS-CoV-2 pandemic, reports began to bring out about co-infections of influenza viruses among themselves and with SARS-CoV-2[39]. The dynamics of transmission, exact progression and clinical manifestations are yet to be well elaborated on and understood for patients suffering from co-infection with SARS-CoV-2 and influenza viruses[40] as shown in Figure 1. However, it is speculated that the use of antiviral therapies for the infection of influenza may improve the prognosis of those having a simultaneous infection with SARS-CoV-2, whereby it increases the burden and affects the efficacy of treatment. All these may be speculated but must be validated to address both cases, with or without concurrent COVID-19 infection[41]. Therefore, this becomes an urgently needed insight into the morbidity and mortality rates among COVID-19 patients who also suffer from other influenza viruses[42].

The increased number and cases of concurrent infections with SARS-CoV-2 and the influenza viruses are now raising much concern to the public health officials and health care providers the world over[43]. First studies on the co-infection rates of COVID-19 and influenza during the co-circulation seasons gave an indication that co-infection was taking place at a low to moderate rate, leaving the findings to be interpreted with caution[44]. For example, the findings of research released in the Journal of Infection pointed out that among those tested for both viruses, a remarkable proportion was found co-infected by the majority of strains[45]. The prevalence rate of co-infection varied with geographic location, testing ability and influenza strain. This variability certainly underlines the difficulty in making a serious estimation of the real prevalence of these coinfections and what impact they really carry for public health[46]. The prevalence of such simultaneous infections suggests that it is primarily influenced by the dynamic nature of viral transmission and the seasonal factors[47]. For example, there was atypically low influenza recording in most places, as the public health interventions included, among others, the very strict interventions such as lockdowns,

social distancing and enhanced hygiene. These, therefore, temporarily altered the expected patterns as to the number of co-infection cases[9,48]. However, since the steps were taken lightly and they continued to circulate, cases of co-infection began to soar, especially in areas witnessing high community transmission of COVID-19 and regions experiencing an outbreak of seasonal influenza[49,50]. The fact that diagnostic tests have varying degrees of accuracy and that some cases may go unreported further supports the idea that the true prevalence of SARS-CoV-2 and influenza co-infection may be greater than what is currently known[51] (Figure 2).

The emerging evidence of dual infections significantly emphasizes the need for comprehensive surveillance systems and increased testing capacity to effectively monitor and react to them[52]. Improved diagnostic tools that can distinguish between and diagnose the co-infections become essential in the view to decide treatment and avoid grave outcomes[53]. Additionally, these results show that one of the key strategies in the mitigation of the risk of co-infection is vaccination[54]. There is hence a need for public health campaigns aimed at sensitizing the vulnerable population on the uptake of the vaccine. As the study unfolds, evidence of the burden and impact of concurrent SARS-CoV-2 and influenza virus infections will remain a fulcrum in responding to and mitigating, controlling respiratory viral diseases[55,56].

Pathogenesis of SARS-CoV-2 and influenza virus

SARS-CoV-2 and influenza viruses are transmitted through similar respiratory routes, the different pathogeneses put into play assure different clinical manifestations and hence have an implication on public health[57]. Both initiate an infection by gaining entry to the upper respiratory tract, where they replicate through available host cell machinery. The virus attaches mainly to the angiotensin-converting enzyme 2 (ACE2) receptor, which is located mainly on the surface of lung epithelial cells and seldom on the surface of other tissues[58, 59] as shown in Figure 3. The

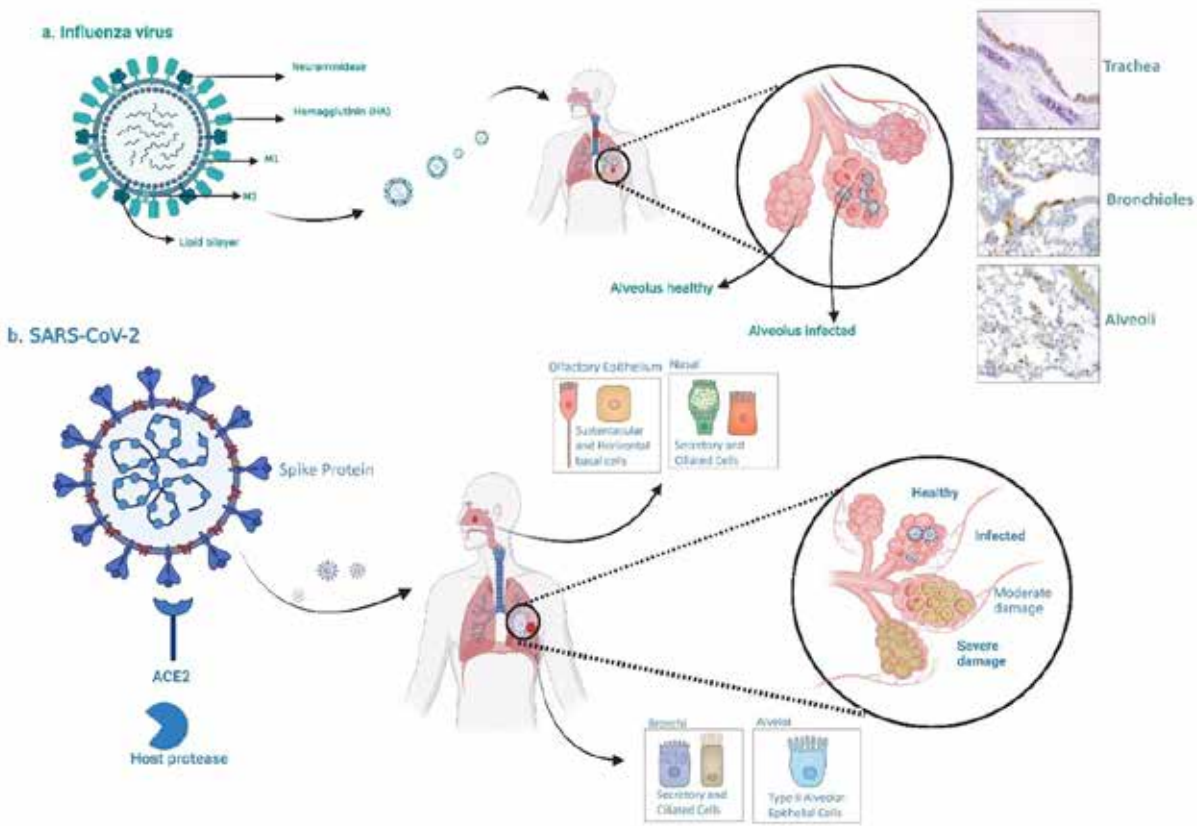

Figure 2: a) The haemagglutinin protein of influenza viruses specifically attaches to sialo saccharides that are present on the surface of pulmonary epithelial cells. Human influenza viruses prefer sialic acid that is connected to galactose by an α 2,6 linkage, whereas avian influenza viruses exhibit a preference for α 2,3 linkage. b) The spike protein of severe acute respiratory syndrome 2 (SARS-CoV-2) attaches to angiotensin-converting enzyme 2 located on the surface of some olfactory and respiratory epithelial cells. Following the activation of ACE2, the process of priming involves the involvement of many cellular proteases such as transmembrane serine protease 2, cathepsin L, neuropilin 1, and furin.

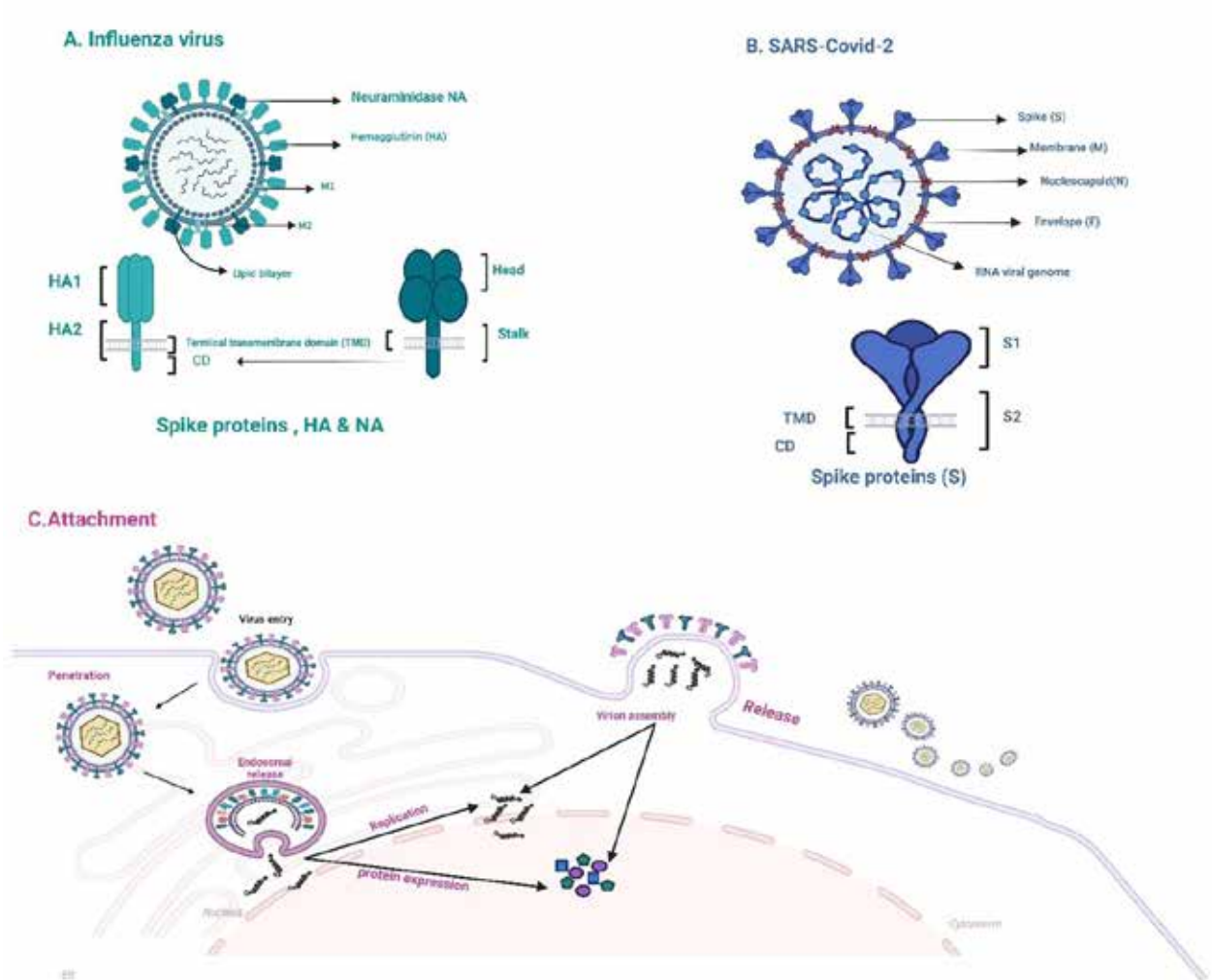

Figure 3: Schematic illustrations A) for Influenza Virus and B) for SARS-CoV-2—both shows, respectively, their spike proteins. Specifically, the head part of the envelope (Env), it is exactly where the hemagglutinin (HA) subunit is and, more importantly, the HA1 for SARS-CoV-2. The stalk parts of these proteins in Influenza are called HA2, and those in SARS-CoV-2 are called S2, analogously to gp41 in other viral contexts. Carrying in its structure Receptor Binding Domain (RBD) and fusion peptides like Fusion Peptide (FP) in head and stalk sections, respectively. According to the classification provided by Baltimore, genomes of Influenza A Viruses (IAVs) and SARS-CoV-2 are, respectively, classified in Groups V and IV. Panel D shows the replication of these viruses in the host cell and consists of elements such as HA, neuraminidase (NA), M1, and M2, which are the proteins in the matrix that act as proton channels in IAVs, and the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins of SARS-CoV-2.

interaction allows the virus to enter the host, where it replicates within the host cells. In contrast, the influenza viruses attach to the sialic acid residues of the surface of epithelial cells of the upper respiratory tract by using hemagglutinin for cell entry and neuraminidase for release of new virions to perpetuate the cycle of the infection[60]. Most importantly, pathogenesis by SARS-CoV-2 involves mainly evading early host immune responses to allow viral loads to reach high titers and cause severe respiratory symptoms[61]. Partial immune evasion includes a decrease in type I interferon responses by many viral proteins that would usually provide an innate immune system for the body against the virus[62,63]. This repression of innate immunity might be one of the reasons for uncontrolled viral replication with later excessive immune response, classically called "cytokine storm"[64]. This hyperinflammatory response is characterized by the excessive release of pro-inflammatory cytokines and chemokines, possibly leading to the development of acute respiratory distress syndrome and multiorgan failure, among other complications[65].

In general, infection by an influenza virus induces more localized lung damage and faster immune responses, while maintaining the capacity to cause serious respiratory illness[66]. Pathogenesis is due to direct cytotoxicity and immune-mediated clearance that continues to be effective in controlling the virus[67]. However, this can sometimes lead to damage of the

lung tissue. Most of the strains usually result in the production of a strong antiviral state in the infected individuals, which is usually mediated by the action of interferons among other cytokines[68]. They serve to limit the spread of the virus but also may be contributors to the sickness feelings of fever, malaise and muscle aches. These two viruses are therefore likely to be related to the cause of complicated risk populations, such as aged people, immunocompromised and patients with existing health conditions[69,70]. For instance, while obesity and diabetes have been considered to have a high relative risk for severe COVID-19, chronic respiratory conditions like COPD have often been reported to have severe outcomes in influenza[71,72]. Beyond this, the spreading and global impact are much more than what is normally seen for most seasonal influenza viruses. This partly relates to the novelty of the virus at the time of the pandemic, thus creating susceptibility across the whole human population and the lack of preexisting immunity[73,74].

Prevalence of SARS-CoV-2 and Influenza Viruses co infections

Between 2019 and 2024, the worldwide health situation was greatly influenced by the widespread spread of SARS-CoV-2 along with influenza virus, each posing distinct difficulties in the administration of public health[75]. The year 2019 experienced the emergence of SARS-CoV-2, which thereafter underwent a rapid spread worldwide that resulted in significant mortality, commonly referred to as the COVID-19 pandemic. Most of this time considered the urgent implementation of new diagnostic techniques, vaccines and therapeutics[76,77]. In contrast, the influenza viruses are present as endemic entities, showing seasonal patterns of their prevalence rates, where the fluctuating rates are probably due to public health interventions issued in order to avoid COVID-19 transmission[78]. Separation of these is uttermost by advanced, virological testing, one of the most important things, due to the similarity in their presenting symptoms but distinct pathogenic ways[79]. Subsequently, the scientific discourse gained momentum as researchers delved into the genetic and molecular traits of these viruses. Effective evaluation would be made of the vaccination against the new developed strain, which has seen a rapid surge in its transmission, and for possible public health consequences arising out of different scenarios of co-infection[80,81]. The study on the patterns of transmissibility and comparison with some useful lessons for future pandemic preparedness was emphasized. Both adaptable health policy frameworks and integrated surveillance systems depended upon were of equal importance[82].

Clinical Outcomes of Concurrent Infections

A case of concurrent influenza and COVID-19 infection is often referred to as "flurona"[186]. In such an era of infectious diseases, the clinical outcomes of the concurrent SARS-CoV-2 (COVID-19) with an influenza virus infection represent a complex challenge, given the overlap in symptomatology and increased risk for combined severe respiratory complications[187,188]. Clinical manifestations have been established with empirical evidence to be even more exacerbated among concomitantly infected patients, including the increased risk of hospitalization and mortalities as compared to singly infected patients[189]. In this way, the dual burden of both viral pathogens amplifies the host inflammatory response to give rise to severe immune dysregulation, which eventually leads to critical illness[190]. The diagnostic dilemma has, therefore, been symptomatic similarities with influenza and COVID-19, which in most instances delay targeted therapeutic measures, complicating clinical management[191]. Effective treatment protocols and strategic resource healthcare allocation during peak transmission periods, therefore, would require understanding this viral interaction and co-pathogenesis clearly[192].

Reviewing cases of co-infection from 2020-2022, a study utilizes public health databases in addition to electronic health records. It might be feasible to estimate the co-infection rate using the predicted rates that these theories suggest using a statistical model if one takes into consideration the independent prevalence of each virus[193]. The results of this analysis confirmed that co-infections did happen, but they primarily affected healthier and younger populations in relation to the clinical outcomes. They did not cause more serious clinical outcomes, such as higher rates of hospitalization, intensive care unit admission or mortality[194]. People who contracted the virus at the same time were more likely to have typical viral symptoms, such as a cough and fever[195]. Continual pandemic monitoring and preparation are of the utmost significance, especially throughout the flu season. Studies suggest that the influence mostly affects the severity of symptoms, despite the fact that coinfection is not more common than expected[196]. So, the research added a lot of new information to our knowledge of the dynamics of respiratory virus coinfections during a pandemic, and how these viruses interact and affect human health. In particular, the understanding of hospitalization and intensive care units (ICU) rates and their implications has been critical, with the severity of concurrent infections of COVID-19 and influenza[197]. Studies showed that when co-infected by both viruses, an exacerbation of acting synergistically is normally experienced by the

co-infected individual, possibly leading to more severe clinical presentations[198]. Data from several health facilities indicate that the general rate of co-infections is generally low. However, the severity of such cases can be high, with much more hospitalization and ICU admission than the patient infected with any of the viruses[199]. They also had higher mortality due to these infections that, through additive or synergistic effects from such concurrent infections, led to an outcome more adverse for the patient. These findings underscore the requirement for energetic diagnostic practice for the early discovery and management of such cases, particularly in the peak of respiratory virus seasons, so that severe outcomes are mitigated, and health care resources are not strained[200].

Impact of Covid and Influenza Concurrent Infections on health care systems

Simultaneous infections of COVID-19 and influenza heighten the burden on healthcare systems to face significant, profound and complex challenges[201]. Such coinfections result in high health service requirements due to worse health outcomes, which overstretch the capacities of hospitals[202]. This complexity in diagnostic procedures can be attributed to the similarity of symptoms and would, therefore, mean that even more resources will have to be put in to distinguish accurately and in time, thus further increasing the operational and financial burdens. Health facilities are presented with the challenge of resource allocation to more isolation units and ICU, therefore disrupting the management of other medical conditions and elective surgeries[203]. Studies have proven the fact that an increase in workload and patient acuity are direct predictors of burnout among healthcare workers. That significantly influences the quality of service delivered to patients[204]. In economic terms, treatment in the case of co-infection is much higher, as it takes longer hospital stays and higher intensity of care, tending to weigh on health budgets and the general economy. Also, managing such effective dual infections will need strong public health policies, including comprehensive dual vaccination drives and dual-testing protocols[205]. This is bound to further add to the pressures the public health systems and policymakers already face in adapting quickly to evolving virus dynamics[206].

Meanwhile, in China, the historic course of influenza seasonality-marked by defined public health intervention during the pandemic-underwent tremendous disruptions from stringent public health actions[207]. China relaxed these measures in 2023, and atypically, that year saw the country face a challenge of an outbreak of influenza. This highlights the need for at least strong monitoring and surveillance to be in place. A national system primarily lays the basis for the public health response in China from following both viruses to provide the much-needed epidemiological data for sound public health management[208,209]. These viruses add to a co-circulation and co-infection that presents a substantial challenge to health systems, from the increased severity of infections. Co-infection, in this case, results in severe clinical outcomes, such as higher hospitalization and admission to the ICUs, and increased mortality, compared to single-virus infection[210]. The fact that co-infections significantly add to the health and economic burden further leads to increased medical cost and extended days of being hospitalized, from an economic point of view. Studies also reveal the decrease in people's vaccination rate against the two illnesses, especially in populations at most risk, despite high COVID-19 vaccination coverage. These thus bring out the highest importance of continued vaccination efforts as a preventive measure to mitigate the impacts from influenza and COVID-19, respectively, underlining dual needs in protection to public health and reduction in the overall disease burden[211,212].

This study highlights the compound challenges that come with concurrent infections of SARS-CoV-2 and influenza viruses. Cases of co-infections by both come with overlapped symptomatology, hence presenting even unique clinical challenges and equitably largely impact the functioning of public health systems due to their co-circulation. The obtained results conclusively prove that the realization of the vaccination strategies, the diagnostic processes and mobilization management warranted a multi-dimensional approach to health and preparedness for public health. We demonstrated a result that co-infection incurs a severe clinical outcome compared to infection by any SARS-CoV-2 or influenza[213]. These findings reflected that a higher proportion was hospitalized, a higher number was admitted to ICUs and mortality had increased. Treatment becomes difficult to manage the two infections due to their clinical management. This often leads to misdiagnoses and treatment with less effective regimens[214]. It is a necessity of healthcare provision to have quick and precise diagnostic tools that can differentiate these viruses and appropriately start treatment in time. This should then be followed by developing comprehensive treatment protocols that bring on board the possibility of coinfections, to manage resources and reduce the burden on healthcare systems. Coinfections are a big problem and should be considered by public health systems, especially during periods of high transmission[215]. Therefore, there is an increased need to provide health care services likely to overstretch health facilities, deplete their resources and

compromise service quality to patients with other conditions other than those caused by either COVID-19 or influenza. Robust planning and health care infrastructure in respect to these eventualities include the surge capacity of the hospitals, critical care resources and health care workforce adaptive strategies for increasing patient loads without getting burned out[216]. Vaccination is an essential measure in controlling the spread of the viruses. Our findings support the necessity of accelerated development and wide deployment of vaccines that would ensure protection from multiple strains of the influenza and SARS-CoV-2 viruses[217]. Such an area remains under continuous research, where vaccination strategies are updated and redevised with new strains. Educational campaigns on public health may advance an increase in the number of vaccinations for persons who remain susceptible to keeping the frequency and severity low in co-infections.

Directions for Future Research

Further research is needed for full comprehension of the dynamics of such co-infections. Longitudinal studies are much needed in order to assess the long-term effects these co-infections have on health outcomes at the individual level and to gain information on when different management becomes effective. More so, genomic studies would detail the interaction of the two persons' viral strains during co-infections and therefore possibly break through the treatment options.

Recommendations

The current study underscores the critical importance of integrated health policies that include enhanced surveillance systems, better diagnostic tools and comprehensive vaccination strategies. They need to further consider that provision includes training for the healthcare providers who bear the first line of responsibility in detecting and managing the diseases. Herein, national and international collaboration is very important, so that the participant countries acquire the latest information and resources to carry out effective combat against the infectious threats.

CONCLUSION

Simultaneous infections by influenza and SARS-CoV-2 not only further complicate clinical care, but also impose significantly challenging impacts on global public health. With this perspective, the systematic review will help and guide future strategies for healthcare preparedness, vaccine development and public health policy. These infections are, therefore, posing dual threats for global health and require collective efforts from researchers, practitioners, policymakers and the public to mitigate the threats in an effective way.

ACKNOWLEDGMENT

We express our heartfelt gratitude to all individuals and the Postdoc office of Jiangsu University whose assistance has made this review possible. We extend our sincere appreciation to Fazal Wahab for his help in statistical analysis. We also wish to express our sincere appreciation to the authors of the referenced papers and the reviewers for their significant efforts.

Conflict of Interest: The authors declare no conflicts of interest.

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Original Article

The role of immature granulocytes percentage to predict severe COVID-19 in children

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Kuwait Medical Journal 2024; 56 (4): 301 - 305

ABSTRACT

Objective: The percentage of immature granulocytes (IG%) has emerged as a novel and readily available parameter of inflammation. No study has investigated the role of IG% in children with coronavirus disease-2019 (COVID-19). We aimed to evaluate the role of IG% in children with COVID-19.
Design: Retrospective analysis
Setting: Mersin University Hospital
Subjects: This study included medical records collected with a prospective design of 266 pediatric patients who applied to COVID-19 triage of pediatric emergency service and 248 sex-age matched healthy subjects.
Intervention: Routine complete blood count parameters including IG% were measured.
Main outcome measure: The receiver operating characteristic curve (ROC) was used to examine the predictive value of IG% in patients with severe and non-severe COVID-19.
Results: Compared with healthy controls, the mean level of IG% was significantly higher in the children with COVID-19 (P<0.01). In COVID-19 group, 39 children had severe disease (17.1%). Compared with non-severe group, IG% was significantly higher in children with severe COVID-19. According to ROC analysis performed for the prediction of severe COVID-19, the best cut-off point for IG% was 0.25% (area under curve=0.697, sensitivity: 71.9%, specificity: 64.3%).
Conclusions: It was first shown that the children with COVID-19 have higher IG% than control subjects. IG% may be helpful for predicting severe disease and it adds information to the conventional infection markers in children with COVID-19.

KEY WORDS: children, COVID-19, immature granulocytes

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a new infectious disease which caused a pandemic worldwide and can lead to acute severe respiratory disease and death[1,2]. The course of COVID-19 in children is different than in adult patients. Since children are potential carriers and spreaders, they are thought to play an important role in COVID-19 as well. Domestic contact is responsible for the majority of contamination in children and therefore asymptomatic carriers are important[3]. In severe cases, pneumonia, severe acute respiratory infection, kidney failure and even death may occur[4].

More recently, the percentage of immature granulocytes (IG%) has emerged as a novel and readily available parameter of inflammation. Automated hematologic analyzer counts can accurately determine IG%. Recent studies have reported that IG has clinical implications in various pathologies such as inflammatory diseases, sepsis and infections[5-7]. There are a few biomarkers of inflammation that use routine laboratory data to evaluate the outcomes of children with COVID-19. On the other hand, no study has evaluated the relationship between IG% and COVID-19 in pediatric population. In the present study, we aimed to evaluate the role of IG% in children with COVID-19.

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SUBJECTS AND METHODS

This retrospective study was conducted after obtaining approvals from the Ministry of Health, Republic of Turkey and Mersin University Clinical Research Ethics Committee (2021-05-05T13-31-52). Medical records were collected with a prospective design of 266 pediatric patients with COVID-19 who applied to COVID-19 triage of pediatric emergency service between March 2020 and December 2020. Nasopharyngeal swab sample was taken from all pediatric patients in accordance with the possible case definition determined by the Ministry of Health and World Health Organization[8,9]. COVID-19 was confirmed with polymerase chain reaction. The severity classification of the disease was made according to the definition of Dong *et al*[10]. In addition, 248 healthy, age- and sex-matched children were included as healthy controls. Children with incomplete medical records, with known hematological diseases, allergic diseases, malignant and inflammatory diseases and receiving drugs that can impact the hematological parameters were excluded from the study.

Patient characteristics and routine complete blood count (CBC) parameters including counts of platelets, neutrophils, lymphocytes and white blood cells, hemoglobin (Hb), IG%, mean platelet volume (MPV) and red blood cell distribution width (RDW) levels were measured. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and mean platelet volume-to-lymphocyte ratio (MPVLR) were calculated.

Statistical analysis

All continuous variables are expressed as mean ± standard deviation. Data of COVID-19 patients and controls were compared. The *t* test, analysis of variance and receiver operating characteristic (ROC) curve were used for statistical analysis. Multiple comparisons were made using one-way ANOVA with post-hoc Tukey's test. The ROC curve was used to examine the predictive value of IG% in patients with severe and non-severe COVID-19. The area under curve was calculated. The appropriate cut-off value of IG% ratio was determined using maximum sum of sensitivity and specificity. The Youden's index was used to determine the cut-off value. The results were considered as statistically significant if *P*-values were less than 0.05.

RESULTS

The characteristics of children with COVID-19 and control groups were shown in Table 1. There was no significant difference between COVID-19 and control groups in terms of the gender, age, Hb, platelet, lymphocyte, MPV, MPVLR and RDW (*P*=0.468, *P*=0.756, *P*=0.920, *P*=0.069, *P*=0.699, *P*=0.136, *P*=0.659 and *P*=0.340, respectively). Compared with healthy controls, the mean levels of white blood cells (WBC), neutrophil, NLR and PLR were significantly lower and IG% was significantly higher in the children with COVID-19 (*P*<0.01, Table 1).

Table 1: Laboratory findings of COVID-19 and control patients.

Characteristics	COVID-19 (n=266)	Control (n=248)	*P*
Age (months)	123.84 ± 69.12	124.68 ± 70.20	0.756
Sex (male/female)	147/119	141/107	0.468
WBC (x10^3/μL)	7.82 ± 3.93	9.76 ± 4.24	<0.001
Hb (g/L)	12.80 ± 1.79	12.77 ± 4.73	0.920
Platelet (x10^3/μL)	275.91 ± 91.33	290.83 ± 94.08	0.069
Lymphocyte (x10^3/μL)	2.76 ± 1.72	2.69 ± 1.90	0.699
Neutrophil (x10^3/μL)	4.11 ± 3.39	5.97 ± 3.93	<0.0001
MPV (fL)	10.25 ± 5.10	9.75 ± 1.28	0.136
MPVLR	5.65 ± 6.61	5.93 ± 7.88	0.659
NLR	2.39 ± 3.61	4.02 ± 6.66	<0.001
PLR	128.71 ± 85.61	158.07 ± 165.43	0.011
RDW (%)	13.89 ± 9.41	13.30 ± 2.02	0.340
IG%	1.22 ± 0.45	0.37 ± 0.22	0.003

WBC: white blood cell; Hb: hemoglobin; MPV: mean platelet volume; MPVLR: mean platelet volume-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; RDW: red blood cell distribution width; IG%: percentage of immature granulocytes

In COVID-19 group, 39 children had severe disease (17.1%). Laboratory results in children with severe and non-severe COVID-19 were shown in Table 2. Levels of WBC, neutrophil, MPVLR, NLR, PLR and IG% were significantly higher and lymphocyte level was significantly lower in severe COVID-19 group (*P*<0.01). According to the ROC curve analysis, the

Table 2: Comparison of laboratory findings of severe and non-severe COVID-19 patients.

Characteristics	Severe COVID-19 (n=39)	Non-Severe COVID-19 (n=227)	*P*
Age (months)	120.65 ± 65.19	125.63 ± 69.78	0.313
Sex (male/female)	23/16	124/103	0.468
WBC(x10^3/μL)	10.13 ± 6.21	7.43 ± 3.25	0.011
Hb (g/L)	12.45 ± 2.22	12.87 ± 1.71	0.276
Platelet (x10^3/μL)	256.80 ± 118.63	279.19 ± 85.67	0.265
Lymphocyte (x10^3/μL)	2.08 ± 1.22	2.87 ± 1.77	0.008
Neutrophil (x10^3/μL)	7.05 ± 5.54	3.61 ± 2.56	<0.0001
MPV(fL)	9.92 ± 0.80	10.31± 5.52	0.669
MPVLR	9.16 ± 12.33	5.05 ± 4.82	0.047
NLR	5.78 ± 7.10	1.81± 2.12	<0.001
PLR	162.57 ± 115.38	122.89 ± 78.25	0.045
RDW (%)	14.05 ± 4.06	13.86 ± 10.05	0.908
IG%	2.68 ± 1.04	0.35 ± 0.67	<0.0001

WBC: white blood cell; Hb: hemoglobin; MPV: mean platelet volume; MPVLR: mean platelet volume-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; RDW: red blood cell distribution width; IG%: percentage of immature granulocytes

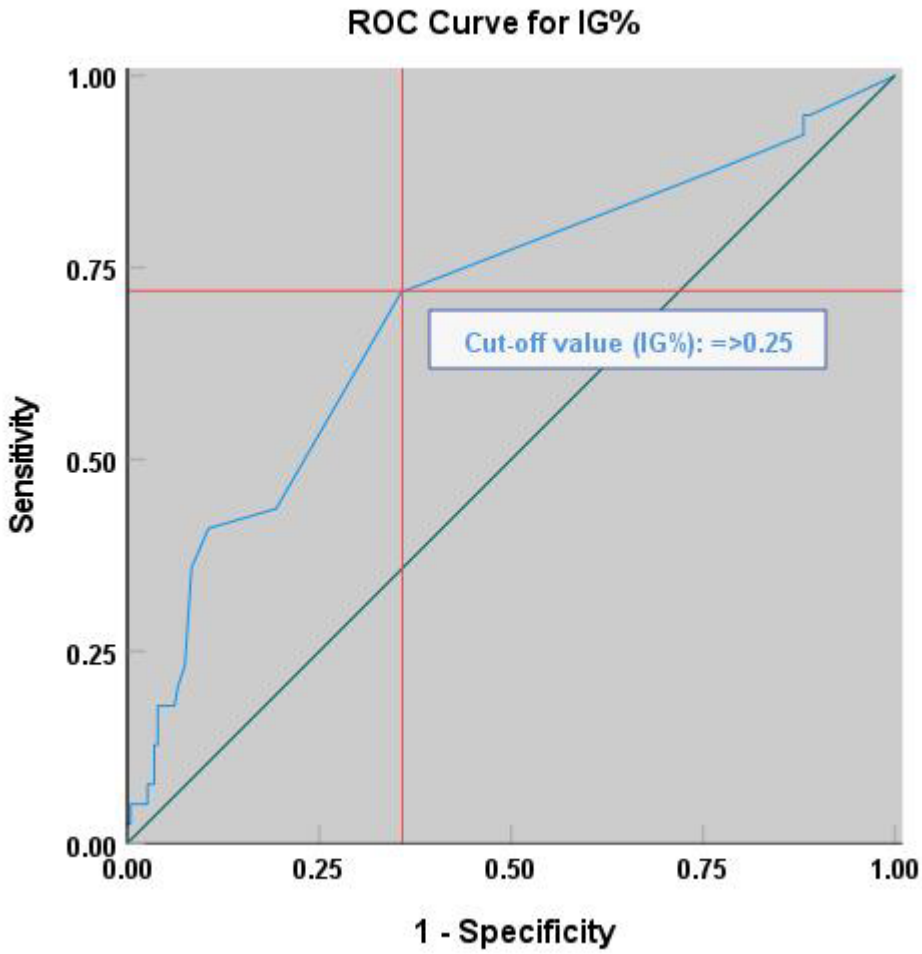

Figure 1: The receiver operating characteristic curve analysis for IG% in the prediction of severe COVID-19 (area under curve=0.697, *P*=0.0001).

best cut-off of IG% for predicting severe COVID-19 was 0.25% with a sensitivity of 71.9%, specificity of 64.3% and accuracy of 65.4% (area under curve= 0.697, Figure 1).

DISCUSSION

To the best our knowledge, this is the first study that has investigated the role of IG% in children with COVID-19. The results of our study indicated that children with COVID-19 had significantly higher IG% than the control subjects. We also demonstrated that level of IG% was significantly higher in children with severe COVID-19 than in those without severe disease.

IG cells include promyelocytes, myolocytes and metamyolocytes that mature along with the myeloid series from the multipotent stem cell located in the bone marrow. While they are not found in peripheral blood under physiological conditions, the bone marrow regulates the production of IG cells in response to inflammatory signals[11]. Recently, modern automated hematology analyzers are available and can measure infection parameters such as IG in addition to CBC. During the past few years, extensive research has been done on IG%, and several studies have emphasized the role of IG% in various forms of inflammatory disease in adult patients. Ayres *et al* demonstrated that IG% are helpful in the exclusion of sepsis diagnosis with a very high specificity[5]. It has been reported that higher IG% levels may correlate with higher disease severity and in-hospital mortality in patients with acute pancreatitis[7]. Nierhaus *et al* found that the total number of IG in peripheral blood from intensive care unit patients is a good marker to discriminate infected and non-infected patients very early during systemic inflammatory response syndrome[12]. They showed that IG% was the highest discriminative value for infection in the first 48 hours in surgical intensive care patients.

Unlike adults, a limited number of studies have investigated the role of IG% in pediatric infectious diseases. Pavare *et al* evaluated whether IG% was a useful predictive marker of severe bacterial infection

in children[13]. They reported that severe infection in children is associated with an increase in IG%. Similarly, highest IG% was found in children diagnosed with sepsis and with bacterial meningitis[14]. Zeng *et al* reported that IG% was the highest for diagnosing coagulase-negative *Staphylococci* in pediatric patients[15]. As the role of IG% has not been defined in children with COVID-19 previously, the studies mentioned above encourage us to assess whether IG% may have a value in COVID-19. We found that IG% was determined to be statistically significantly high in children with COVID-19 compared with the healthy control group. We also observed that IG% levels were higher in children with severe COVID-19. In the ROC that was done to determine the severity of COVID-19, the cut-off value of IG% was found as 0.25% with a sensitivity of 71.9%, specificity of 64.3% and accuracy of 65.4%.

There are a few biomarkers of inflammation that use routine laboratory data to evaluate the outcomes of COVID-19 in children[16,17]. Henry *et al* reported that consistent pattern of laboratory derangements has yet to be observed in children with confirmed COVID-19[16]. They reported that the majority of patients had normal neutrophil counts, with only 4.6% above the normal range and 6% below the normal range. On the other hand, Bourkhissi *et al* found that a normal leukocyte count was found in 94% of children, with 4.4% of them having leucopoenia and 1.6% of them having hyperleukocytosis[18]. They reported that neutropenia was found in 7% of children and only 3% of them had lymphopenia. In the current study, we found that the mean levels of WBC, neutrophil, NLR and PLR were significantly lower compared with control group. We also showed that levels of WBC, neutrophil, MPVLR, NLR and PLR were significantly higher and lymphocyte level was significantly lower in severe COVID-19 group.

This study had several limitations. First, this study was designed as retrospective in nature. Second, the number of patients with severe COVID-19 was relatively low. Third, we did not evaluate fluctuations in IG%. On the other hand, our study has several strengths as well. This is the first to examine the value of IG% in children with COVID-19. IG% is a simple parameter provided mostly by readily available automatic hematology analyser.

CONCLUSION

In conclusion, the results of this study show that the children with COVID-19 have higher IG% than control subjects. In addition, IG% may be helpful for predicting severe disease and it adds information to the conventional infection markers in children with COVID-19.

ACKNOWLEDGMENT

Author contribution: Gulcin Bozlu, Berfin Ozgokce Ozmen, Mehtap Akca and Fatma Durak conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Necdet Kuyucu carried out the initial analyses, reviewed and revised the manuscript and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Conflict of interest declaration: Our study has not received any financial support. Further, the authors declare that no conflict of interest exists.
Sources of support: None
Disclosure of funding: None

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Original Article

Ultrasonographic diagnosis of antral gastritis: The hypoechoic halo sign

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Kuwait Medical Journal 2024; 56 (4): 306 - 310

ABSTRACT

Objective: The aim of the study was to evaluate the hypoechoic halo sign, a finding that can be used in the ultrasonographic diagnosis of antral gastritis, and its relationship with clinical symptoms.
Design: Retrospective analysis of prospectively collected data
Setting: Erzincan Binali Yildirim University Mengucek Gazi Training and Research Hospital, Erzincan, Turkey
Subjects: The study included 39 patients with endoscopically proven antral gastritis and 39 age- and sex-matched controls with an endoscopically normal antrum.
Intervention: The hypoechoic halo sign was defined as a hypoechoic band surrounding the echogenic middle part of the antrum in axial ultrasonographic images.
Main outcome measures: The presence of heartburn, dyspepsia, reflux and nausea and the visual pain scale (VAS) scores of the patients were recorded.
Results: The hypoechoic halo sign was observed at a rate of 84.6% in the antral gastritis group, while this rate was 15.4% in the control group (P<0.001). The receiver operating characteristic curve analysis showed that the thickness of the hypoechoic halo being larger than 6.7 mm was associated with antral gastritis at a sensitivity of 87.9 and specificity of 100. The univariate analysis showed that age, steatosis, heartburn, dyspepsia, VAS score, reflux and nausea were associated with the thickness of the halo sign.
Conclusion: The hypoechoic halo sign can be used with high specificity and sensitivity in the diagnosis of antral gastritis.

KEY WORDS: antral gastritis, hypoechoic halo sign, ultrasonography

INTRODUCTION

Gastritis is the inflammation of the gastric mucosa leading to various clinical symptoms, such as nausea, dyspepsia, epigastric pain and vomiting. *Helicobacter pylori* infection is the most common cause of gastritis[1]. *H. pylori* causes an increase in the thickness of the mucosal, submucosal and muscularis mucosal layers, resulting in an increase in the gastric wall thickness. Gastritis can be evaluated clinically, radiologically, endoscopically and histopathologically[2].

Transabdominal ultrasonography is a very useful method for the non-invasive and physiological examination of the gastrointestinal tract[3]. It has been shown to have good accuracy and reproducibility not only in the primary examination but also in the follow-up of chronic diseases[4]. Ultrasonography is a non-invasive, easily accessible, safe and inexpensive option for imaging the stomach. However, despite all these advantages, the use of ultrasonography in gastric evaluation is limited[5].

The aim of this study was to evaluate the hypoechoic halo sign, a finding that can be used in the ultrasonographic diagnosis of antral gastritis, and its relationship with clinical symptoms.

SUBJECTS AND METHODS

This study was approved by the Institutional Ethics Committee for the retrospective evaluation

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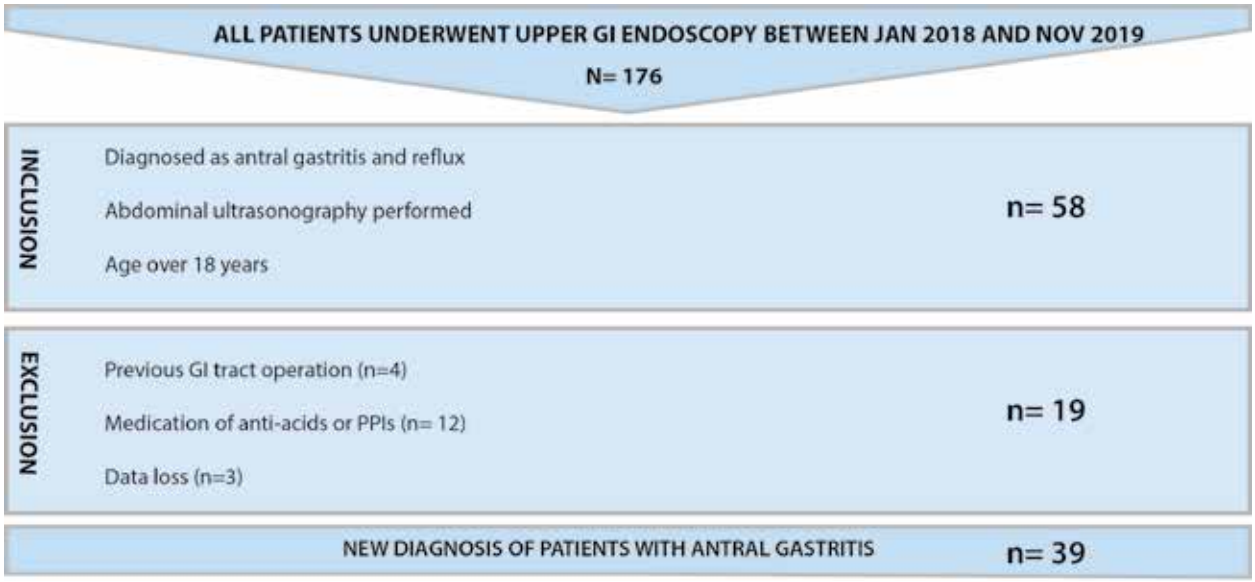

Figure 1: Flowchart showing the inclusion/exclusion criteria of the study

of prospectively collected data from January 2018 to December 2018. Informed consent was obtained from all participants.

Patients

Thirty-nine patients with endoscopically proven antral gastritis and 39 age- and sex-matched controls with an endoscopically normal antrum were included in the study. The inclusion and exclusion criteria are shown in Figure 1. The presence of heartburn, dyspepsia, reflux and nausea was recorded among the symptoms of the patients. In addition, the visual pain scale (VAS) was used to evaluate epigastric pain. The control group consisted of *H. pylori*-negative individuals with no previous diagnosis of upper gastrointestinal symptoms.

Ultrasound examination

The ultrasonographic evaluation (Aplio 500 ultrasound system, Toshiba Healthcare, Tokyo, Japan) was performed by a radiologist with five years' experience in the morning before the endoscopic examination. A 5 MHz convex transducer was used to evaluate the antrum in the epigastric region. All the patients were given 500 ml of water before the examination to ensure that the luminal borders were clear. The patients were examined first in the supine position, and then in the right lateral decubitus position. The gastric antrum and trunk were examined in sagittal and axial planes by sliding the probe, which had been inserted into the epigastric region, from right to left. The antrum was visualized in the parasagittal plane immediately to the right of the midline using the left lobe of the liver as an acoustic window. The hypoechoic halo sign was defined as a hypoechoic band surrounding the echogenic middle part of the antrum in axial images (Figure 2). The halo thickness was also measured in patients with this finding.

Statistical analysis

Summary statistics were reported as mean ± standard deviation. The distribution of normality was assessed with the Shapiro-Wilk test. Nominal categorical variables are assessed with the chi-square test. The receiver operating characteristic (ROC) curve

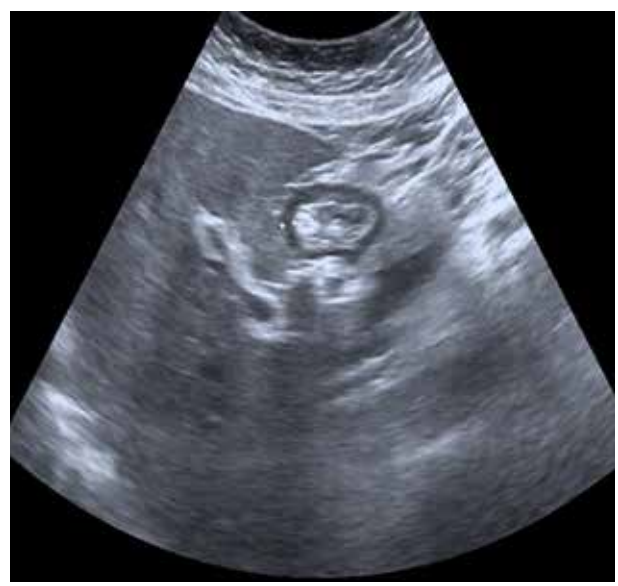

Figure 2: Ultrasound image showing the hypoechoic halo sign acquired in the axial plane at the level of the gastric antrum

analysis was conducted to detect the cut-off value of the thickness of the hypoechoic halo with the best possible sensitivity and specificity. The univariate and multivariate regression analyses were performed to identify independent variables associated with the hypoechoic halo sign. A two-tailed *P*-value of <0.05 was accepted as statistical significance. All statistical analyses were performed via the R statistical software package (R studio, Vienna, Austria).

RESULTS

The mean age of the study population was 47.8±12.4 years, and the female-to-male ratio was 1.05 (20/19). Of the 39 patients with antral gastritis, 33 had the hypoechoic gastric halo sign (84.6%), whereas this finding was not detected in the remaining six (15.4%) patients in this group. In the control group, the halo sign was observed in five (12.8%) patients, and it was not present in 34 (87.2%). A statistically significant difference was found between the two groups in terms of the presence of the hypoechoic halo sign (*P* <0.001).

The mean thickness of the hypoechoic halo was 7.8±1.8 mm. The ROC curve analysis showed that the thickness of the hypoechoic halo being larger than 6.7 mm was associated with antral gastritis at a sensitivity of 87.9 and specificity of 100, and the area under the curve was calculated as 0.964 (Figure 3).

The univariate analysis showed that age, steatosis, heartburn, dyspepsia, VAS score, reflux and nausea were associated with the thickness of the halo sign (Figure 4). The multiple regression analysis showed that age [estimate/standard error (SE)=0.03/0.01, *P*=0.012], reflux (estimate/SE=0.88/0.38, *P*=0.027), and VAS score (estimate/SE=0.40/0.11, *P*=0.001) were independently associated with the thickness of the hypoechoic halo sign.

DISCUSSION

The most important result of our study is the significantly higher rate of the hypoechoic halo finding in patients with antral gastritis. In addition to the halo sign, its thickness has been shown to be important in antral gastritis. Steatosis, heartburn, dyspepsia, VAS score, reflux and nausea have also been associated with the halo sign. In a recent study by Zaher *et al*, it was shown that the antral wall thickness was higher in patients with antral gastritis than in the control group[6]. In another study, Jadhav *et al* showed that the wall thickness was higher in patients with mild antral gastritis compared to the control group[7]. Cakmakci *et al* reported that there was wall thickening sonographically in antral gastritis due to the *H. pylori* infection, even if there was no endoscopic finding of gastritis[8]. These findings are also supported by our

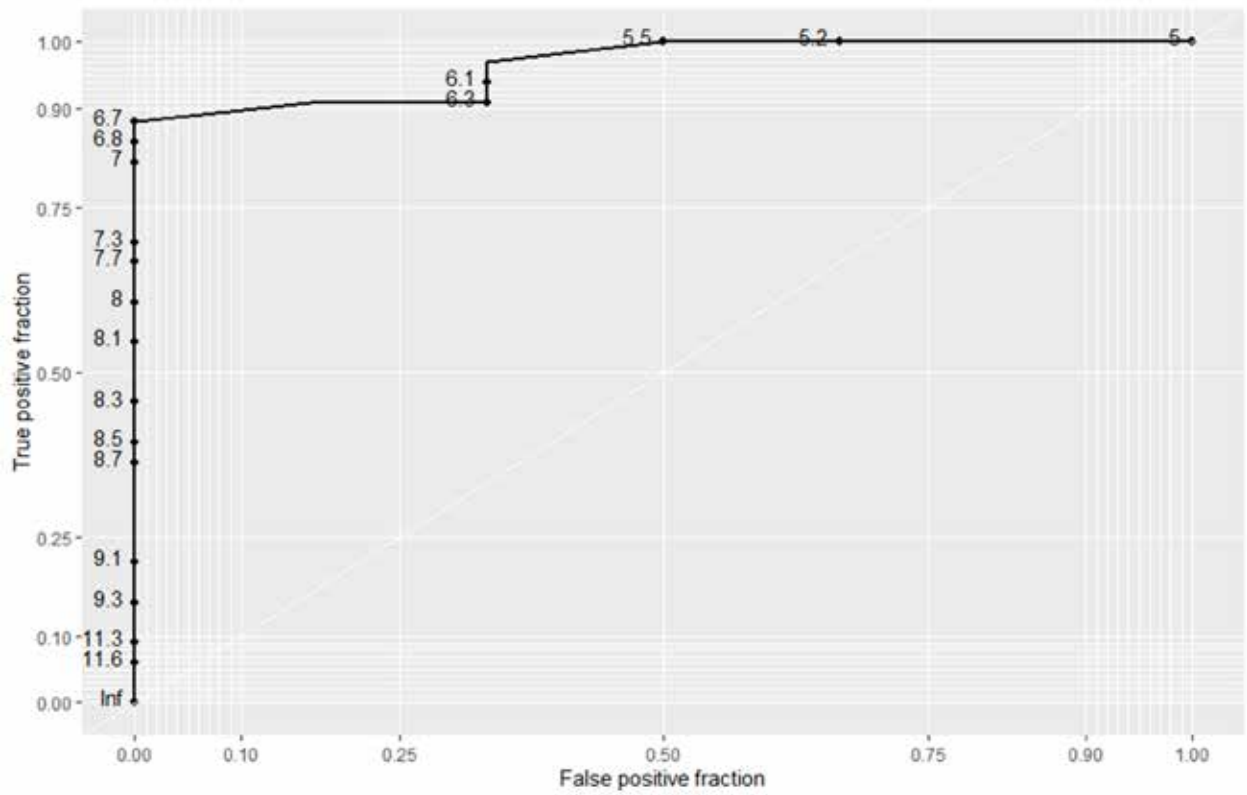

Figure 3: Receiver operating characteristic curve of the hypoechoic halo thickness for the diagnosis of antral gastritis

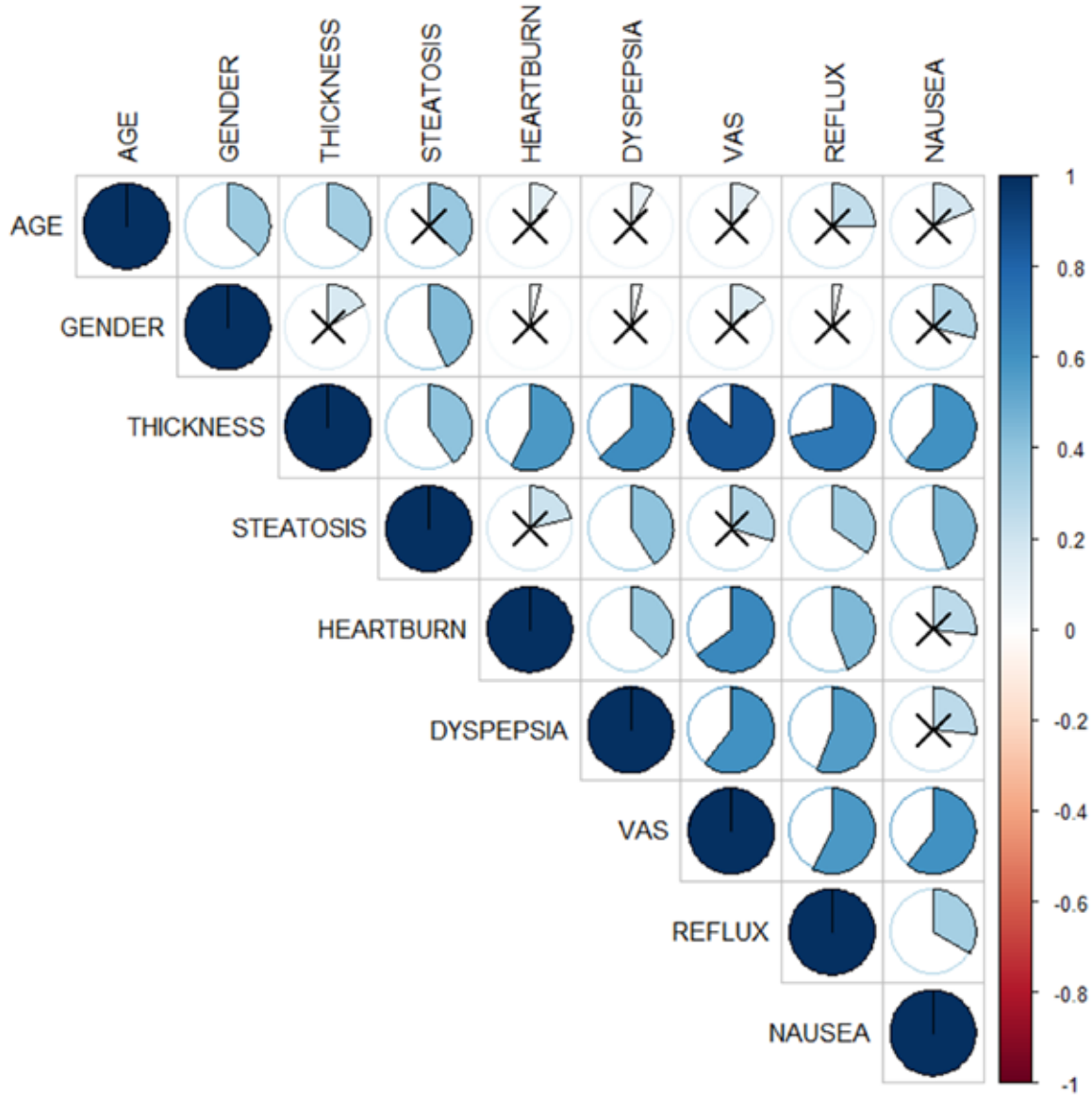

Figure 4: Pie-shaped correlation plot showing the results of the univariate analysis of associated variables (X denotes correlations with *P*-values higher than 0.05)

results. Moreover, in our study, an ultrasonographic finding that could be used in the diagnosis of antral gastritis was defined for the first time in the literature.

The *H. pylori* infection often begins in the antrum, where acidity is less than in the corpus. It is usually located in the deep layers of the mucosa and the superficial part of the muscularis mucosa. The colonization of *H. pylori* in the stomach can cause gastric wall inflammation, increased gastrin secretion, and gastric acid production, which all ultimately lead to gastritis[9]. In gastritis, inflammatory degeneration and compensatory regeneration of the mucosal layer are seen together. Depending on the region where gastritis occurs and the severity of the damage, diseases such as duodenal ulcer, gastric ulcer, atrophic gastritis and stomach cancer may also occur[10]. Therefore, the early diagnosis of antral gastritis is very important for the appropriate management of the disease[11]. Endoscopy is often performed when patients develop dyspeptic symptoms. However, endoscopy is an invasive procedure with no diagnostic reference standard[12]. In our study, the relationship between clinical findings and the hypoechoic halo sign was shown. Therefore, we consider that the hypoechoic halo sign will be beneficial in the ultrasonographic diagnosis of antral gastritis.

Transabdominal ultrasonography is a non-invasive method for evaluating gastric and

duodenal wall layers and measuring their thickness. The ability of ultrasonography to evaluate transmural inflammatory disorders is a significant advantage over contrast radiography[13]. Ultrasonography can also be used effectively in the evaluation of the stomach. In a study by Nylund *et al*, the mean gastric antrum thickness in the healthy population was found to be 2.9 mm[14]. In our study, it was shown that a hypoechoic halo thickness of greater than 6.7 mm in the antrum had 87.9% sensitivity and 100% specificity in the diagnosis of antral gastritis.

Our study had certain limitations. First was the small number of patients. More extensive studies are needed in this area. Second, the ultrasonographic evaluation and measurements were performed by a single radiologist. Therefore, possible inter-observer differences could not be evaluated.

CONCLUSION

Our study revealed that the hypoechoic halo finding observed in ultrasonography can be used with high specificity and sensitivity in the diagnosis of antral gastritis. This finding may be useful in diagnosing gastritis cases requiring further investigation and avoid unnecessary interventions.

ACKNOWLEDGMENT

Disclosure statement: All authors declared no conflict of interest.

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Original Article

Efficacy of erector spinae plane block versus deep serratus plane block for post-operative analgesia following modified radical mastectomy: a randomized controlled study

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Kuwait Medical Journal 2024; 56 (4): 311 - 316

ABSTRACT

Objectives: The study aimed to compare postoperative morphine consumption and analgesic profile of the two ultrasound blocks; erector spinae block and serratus anterior block following modified radical mastectomy.
Design: Randomized controlled study
Setting: King Saud medical city, King Saud University, Riyadh, KSA
Subjects: The study was conducted on 81 adult patients scheduled for elective modified radical mastectomy.
Intervention: Patients were randomized to receive either serratus anterior block (n=41) or erector spinae block (n=40).
Main outcome measures: Cumulative total and time course of morphine consumption 24 hours after surgery. The secondary outcomes were the numerical rating scale pain score, nausea and vomiting and the time to mobilization during the first 24 hours postoperatively.
Results: Total morphine consumption (mean +/- SD) was significantly higher in the serratus anterior group compared to erector spinae group (3.44+/-2.82 mg vs. 2.28+/-1.61 mg, *P*=0.026). Time course morphine consumption was significantly higher in serratus anterior group only at 4 and 24 hours compared to erector spinae group (0.56+/-1 vs. 0.1+/-0.37, *P*=0.01; 1.73+/-1.51 vs. 1.05+/-1.06, *P*=0.037). Numerical rating scale pain score was higher in serratus anterior group at 0, 1 and 4 hours compared to erector spinae group (0.73+/-1.11, 1.10+/-1.02, 1.44+/-1 vs. 0.23+/-0.8, 0.93+/-1.02; *P*<0.0001, *P*=0.001, *P*=0.029). Times to mobilization, nausea and vomiting postoperatively were not significantly different in both groups (*P*<0.05).
Conclusion: Compared to serratus anterior group, erector spinae group had less morphine consumption and better analgesic profile 24 hours following modified radical mastectomy.

KEY WORDS: erector spinae, mastectomy, serratus, ultrasound

INTRODUCTION

Modified radical mastectomy (MRM) is one of the most common breast surgical procedure[1]. Nearly 60% of the patients reported moderate to severe pain in the post-operative period[2]. Incomplete postoperative pain relief can lead to the development of chronic pain syndrome[3]. Therefore, pain following MRM should be effectively controlled with multi modal analgesia regimen (MMA). Regional analgesia is a major part of MMA and enhances recovery by reducing the need for postoperative opioids[4]. Recently, many interfascial plane blocks have been described[5-9]. New ultrasound (US) guided regional block techniques have been used effectively to provide analgesia following MRM. Studies in the literature showed that US guided erector spinae plane block (ESPB) and serratus anterior plane block (SAPB) are effective analgesic techniques for this purpose[10-12]. Both blocks involve deposition of local anesthetic (LA) in an interfascial plane away from sensitive structures like spinal cord, major vessels and pleura, and technically they are considered easier than thoracic epidural or paravertebral block. More recently, deep serratus anterior plane block (DSAPB) which involves injecting LA deep to the serratus

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anterior muscle, has been reported to be an effective regional analgesic technique[13]. Given the nature of the ESPB and proximity to neuraxis relative to the DSAPB, we hypothesized that analgesic efficacy of ESPB would be better compared to DSAPB. This prospective randomized study aims to compare the efficacy of ESPB and DSAPB for postoperative morphine consumption after MRM.

SUBJECTS AND METHODS

Approval of this study protocol was provided by the research ethical committee at King Saud Medical City (King Saud University, Riyadh, KSA), reference number E-19-3943 dated April 25, 2019. The study was preregistered on clinicaltrial.gov, reference number NCT04108715. Written informed consent was taken from 81 ASA physical status I-II female patients aged 37-68 years and scheduled to undergo elective MRM. The study was conducted between April 2020 - March 2021 in our hospital. Exclusion criteria were previous breast surgery, coagulopathy, spine abnormality, infection at the proposed injection site, age >70 years and body mass index (BMI) >40 kg/m^2. The primary outcomes of this study were to compare cumulative total morphine consumption of the two blocks, and time course of morphine consumption at 0, 1, 2, 4, 8 and 24 hours postoperatively. The secondary outcomes were numeric rating scale (NRS) pain score, postoperative nausea and vomiting (PONV) and time to initial patient mobilization. Patients were randomly allocated into two groups (ES and SA) using a computer-generated list of random numbers and sealed envelopes. The ES group (n=40) had ESPB at the thoracic spinous process T5 level and the SA group (n=41) had DSAPB at a level of the 5th rib over the mid-axillary line. Blocks were performed by the same anesthetist. During preoperative visit, all patients were educated on how to use patient-controlled analgesia (PCA) and NRS for assessing pain severity, with a score from 0-10 (0: no pain, 10: most severe pain). Patients were instructed to press the patient-controlled analgesia (PCA) button when NRS score >3. Intravenous (IV) access was established, and no premedication was given.

Intraoperative procedures

ASA standard monitoring was connected, and general anesthesia was intravenously induced with propofol (2.5 mg/kg), fentanyl (2 mcg/kg), and the trachea was intubated after administration of rocuronium (0.7 mg/kg). Anesthesia was maintained with sevoflurane (1-1.5 MAC) and oxygen (40%). IV paracetamol (15 mg/kg) with dexamethasone (0.1 mg/kg) was administered.

The US guided block was performed with the patient in the lateral decubitus position and the surgical side being the upper side, after induction of general anesthesia in both groups, using a linear probe 6-15 MHZ (M-Turbo, SonoSite Inc., USA) covered with a sterile sheath and sterile US gel. A nerve block needle (22-G, 50 mm/100 mm Sonoplex, Pajunk, Geisingen, Germany) was used in an in-plain technique. For SA group, after skin disinfection with chlorhexidine gluconate in isopropyl alcohol 70%, US probe was placed in a sagittal plane over the 5th rib at the mid-axillary region to identify the Latissimus dorsai muscle and deeper to it, the serratus anterior muscle overlying the ribs, which appears as rounded hyper-echoic structure. The needle is inserted in a caudad-cephalad direction till it hits the rib, after careful aspiration and injection of 2 ml saline, bupivacaine 0.25% (0.4 ml/kg) was injected.

For the ES group, the US probe was placed over a sagittal plane 2 centimeters lateral to the 5th thoracic spinous processes to identify the hyper-echoic transverse process with acoustic shadow, and three muscle layers: trapezius muscle, rhomboid muscle and erector spinae muscle superficial to the transverse process. After skin disinfection, the needle is inserted in plane in a caudad-cephalad direction to its destination upon contacting the transverse process. After careful aspiration and injection of 2 ml saline, bupivacaine 0.25% (0.4 ml/kg) was injected. All interfascial plane blocks are routinely performed while the patient is under general anesthesia in our hospital; therefore, patients were not aware of their group allocation. Upon completion of surgery, IV ondansetron 4 mg with neostigmine 50 mcg/kg and glycopyrrolate 400 mcg was administered. The trachea was extubated after achieving full recovery parameters, and the patients were sent to post anesthesia care unit (PACU) where 0 time is estimated on admission.

Post-operative procedures

The PACU nurse attached PCA pump to the patients. The pump setting was morphine 1 mg/ml, bolus dose 1 mg, lockout interval of 10 minutes and a maximum dose of 5 mg/h. Pain was assessed by PACU/ward nurses who were not aware of the type of block. They used the NRS score to assess the pain at 0, 1, 2, 4, 8 and 24 hours after surgery and recorded the data on the study sheet. Paracetamol 15 mg/kg was administered IV every 8 hours. Morphine consumption and opioids related side effects (PONV, respiratory depression and itching) and time to first mobilize were recorded at 0, 1, 2, 4, 8 and 24 hours. Breakthrough pain was defined as NRS score >4 while patients on PCA and was treated with tramadol 50 mg IV bolus up to 100 mg as needed. Respiratory depression was defined as respiratory rate <8/min or pulse oximeter showing SPO_2 <92%. PONV was treated with ondansetron 4 mg IV.

Statistics and sample size calculation

The sample size calculation were performed using Power and Sample Size Calculation (version 3.1.2; Vanderbilt University, Nashville, Tennessee). Assuming type I error of 0.05 with 80% power to detect the difference, a sample size of 38 patients were required in each group, based on 15% difference in morphine consumption between the 2 groups. To account for missing patient data and dropout, 90 patients were enrolled for the study (forty-five in each group). Statistical analyses were performed with SPSS software (version 20.0; IBM Corporation, Armonk, New York). Data were entered as numerical or categorical, as appropriate. Distribution of variables were tested according to Kolmogorov-Smirnov test. Data with normal distribution between the study groups were compared using unpaired *t* test and described as minimum, maximum and mean with standard deviation. Data with non-normal distribution were compared using Mann-Whitney *U* test. Fisher test was used to compare categorical data.

Table 1: Patient's demographic data and characteristics

Parameters	Group		*P*-value
	ES (n=40)	SA (n=41)	
ASA			0.165
I	9 (22.5%)	15 (36.6%)	
II	31 (77.5%)	26 (63.4%)	
Age	46.80 ± 7.498	50.22 ± 8.132	0.067
BMI	30.11 ± 4.033	31.505 ± 4.383	0.140
BMI classification			0.547
Normal weight	3 (7.5%)	1 (2.4%)	
Overweight	18 (45%)	18 (43.9%)	
Obese	19 (47.5%)	22 (53.7%)	

ES: erector spinae plane block group; SA: serratus anterior plane block group; ASA: American society of anesthesiologist; BMI: body mass index

RESULTS

Ninety patients undergoing elective MRM were initially assessed for eligibility. Nine patients were excluded for the following reasons: age >70 yrs (n=1), morbid obesity BMI >40 kg/m^2 (n=5), ASA >II (n=2) and PCA related technical problem (n=1). Eighty-one patients completed the study, patients' characteristics of the two groups (ES; n=40, SA; n=41) were comparable (Table 1). Total PCA morphine consumption (mean +/- SD) was significantly higher in the SA group compared to ES group (3.44+/-2.82 mg vs. 2.28+/-1.61 mg, *P*=0.026) (Table 2, Fig 1). Morphine consumption was significantly higher in SA group only at 4 and 24 hours compared to ES group (0.56+/-1 vs. 0.1+/-0.37, *P*=0.01; 1.73+/-1.51 vs. 1.05+/-1.06, *P*=0.037) (Table 3, Fig 2). NRS pain score was higher in SA group at 0, 1 and 4 hours compared to ES group (0.73+/-1.11, 1.10+/-1.02, 1.44+/-1 vs. 0.23+/-0.8, 0.93+/-1.02; *P* <0.0001, *P*=0.001, *P*=0.029) (Table 4, Fig 3). Time to first mobilize postoperatively and PONV was not significantly different in both groups. No complications were recorded related to the blocks.

Table 2: Cumulative total morphine consumption

Variable	Group		*P*-value
	ES (n=40) Mean ± SD Median (Min – Max)	SA (n=41) Mean ± SD Median (Min – Max)	
Total of morphine consumption (mg)	2.28 ± 1.617 2.0 (0-5)	3.44 ± 2.82 3.0 (0 -11)	0.026

ES: erector spinae plane block group; SA: serratus anterior plane block group; SD: standard deviation
P-value statistically significance <0.05

DISCUSSION

Our current randomized controlled study compared ESPB with DSAPB for postoperative cumulative and time course morphine consumption after MRM and found that ESPB had lower cumulative morphine consumption and lower morphine consumption at 4 and 24 hours postoperatively. The analgesic profile (NRS score) of the ESPB was better than DSAPB for the first four hours postoperatively. The results were in accordance with our hypothesis; the closer the block to the neuraxis, the more effective is the block.

MRM with or without axillary lymph nodes dissection is one of the most common types of cancer- related surgery in female patients. The breast is innervated by supraclavicular nerves, which is a

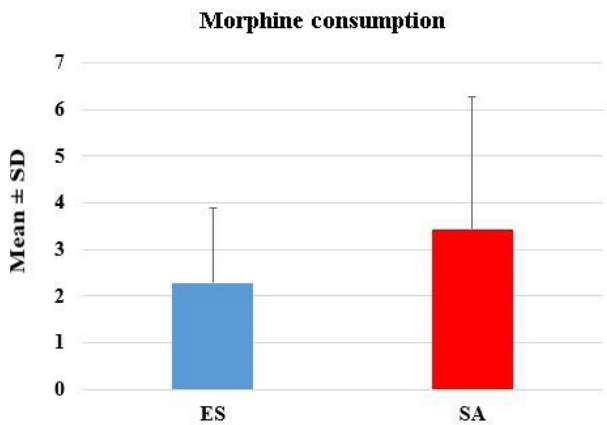

Figure 1: Cumulative total morphine consumption

Table 3: Time course of morphine consumption

Block type ES/SA	Morphine consumption (mg)					*P*-value
Time	0 hr	1 hr	4 hr	8 hr	24 hr	
ES	0.08 ± 0.35 0 (0-2)	0.08 ± 0.35 0 (0-2)	0.10 ± 0.379 0 (0-2)	0.85 ± 1.001 0 (0-3)	1.05 ± 1.061 1 (0-3)	< 0.0001
SA	0.07 ± 0.346 0 (0-2)	0.10 ± 0.436 0 (0-2)	0.56 ± 1.001 0 (0-4)	0.95 ± 1.139 0 (0-4)	1.73 ± 1.517 2 (0-5)	< 0.0001
P value	0.980	0.999	0.010	0.785	0.037	

ES: erector spinae plane block group; SA: serratus anterior plane block group; SD: standard deviation
P-value statistically significance <0.05 at 4h and 24h.

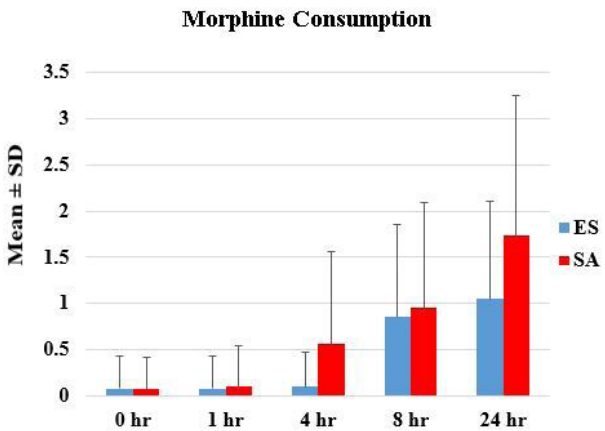

Figure 2: Time course of morphine consumption

branch of the cervical plexus, and by the lateral and anterior branches of the second to sixth intercostal nerves[14]. The complex innervation of the breast makes post-operative analgesia more difficult, and no single block could achieve complete pain control. Therefore, MMA regimen with the interfascial plane blocks like ESPB and SAPB is an important choice[15]. ESPB was first described by Forero *et al* for treating chest wall neuropathic pain[9]. Although the mechanism of ESPB in producing extensive sensory block is not clear, a magnetic resonance imaging study showed that injected LA with gadolinium beneath the erector spinae fascia diffused to the paravertebral space and spinal canal[16]. A recent meta-analysis demonstrated that pain score and opioid consumption were significantly reduced in patients receiving ESPB after breast surgery[17]. The result of this analysis suggested that LA could block the ventral and dorsal rami of the thoracic spinal nerves.

SAPB was first described by Blanco *et al*, as a modification of PECs II block[8]. The LA is deposited between the serratus anterior and latissimus dorsai muscles to block the lateral branch of the intercostal nerves and provide sensory blockade of the T2-T9 dermatomes[18].

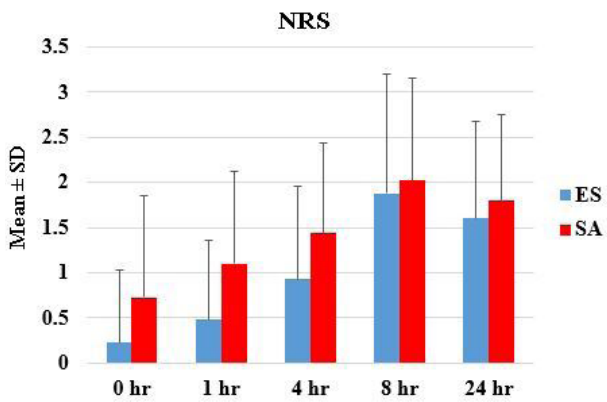

Figure 3: Numerical rating scale NRS (0-10) pain score

Table 4: Numerical rating scale (NRS) pain score

Block type ES/SA	NRS					*P*-value
Time	0 hr	1 hr	4 hr	8 hr	24 hr	
ES	0.23 ± 0.8 0 (0-4)	0.48 ± 0.877 0 (0-3)	0.93 ± 1.023 0 (0-3)	1.88 ± 1.324 2 (0-4)	1.6 ± 1.08 2 (0-3)	< 0.0001
SA	0.73 ± 1.119 0 (0-6)	1.10 ± 1.02 1 (0-4)	1.44 ± 1.0 2 (0-3)	2.02 ± 1.129 2 (0-5)	1.8 ± 0.954 2 (0-4)	< 0.0001
P value	< 0.0001	0.001	0.029	0.755	0.657	

ES: erector spinae plane block group; SA: serratus anterior plane block group; SD: standard deviation

Chen *et al* reported that SAPB provided significantly less opioid consumption and lower pain score up to 8 hours compared to LA infiltration after thoracoscopic surgery[19]. Further modification to SAPB termed the serratus intercostal fascial plane involves deposition of LA deep to the serratus anterior muscle, which we have used in our study (DSAPB). The close proximity of the injected LA to the intercostal nerve is one of the proposed advantages compared to the superficial SAPB[20].

Both ESPB and DSAPB are relatively superficial interfascial plane blocks, safe and easy to perform under US guidance[21]. Finnerty *et al* published a study comparing ESPB versus SAPB for minimally invasive thoracic surgery and found ESPB provided superior quality of recovery and better analgesia[22]. LA volume and concentration is an important determinant of the block extension and duration. A study on the use of SAPB for breast surgery showed that 40 ml of 0.375% ropivacaine had more extensive block than 20 ml[23]. One of the limitations of our study was that the blocks were carried out after induction of general anesthesia; therefore, we couldn't assess the sensory dermatomal level or block function.

CONCLUSION

In conclusion, ESPB was more effective than DSAPB in reducing morphine consumption following MRM.

ACKNOWLEDGMENT

I thank Prof. Ahmed Abdul Momen, Prof. Abdul Aziz Al Saif, Dr. Ali ALWahabi and the statistician Mr. Ameer Marzouk for helping me to conduct this study.

Conflict of interest: There is no conflict of interest.

Financial support and sponsorship: Nil

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Original Article

A novel marker for predicting the development of contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention: platelet-hemoglobin ratio

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Kuwait Medical Journal 2024; 56 (4): 317 - 324

ABSTRACT

Objective: In coronary artery diseases and heart failure, platelet-hemoglobin ratio (PHR) has been proven to have a predictive value. We aim to study the relationship between PHR and contrast-induced nephropathy (CIN).
Design: Retrospective study
Setting: University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital
Subjects: A total of 1513 patients were included in the study. The patients were divided into two groups, those with and without CIN.
Interventions: Percutaneous coronary intervention and CIN
Main outcome measures: PHR, platelet count, hemoglobin, serum troponin, N-terminal proBNP (NT-proBNP), creatinine and 48-72 hours creatinine levels were assessed.
Results: CIN developed in 265 (17.5%). Atrial fibrillation (AF), diabetes mellitus, hypertension (HT), hyperlipidemia and heart failure are more common (P<0.001, P<0.001, P<0.001, P=0.043, P=0.008, respectively); and PHR (1.94±0.96 vs. 2.13±0.95, P=0.005), peak creatinine kinase–myocardial band (CK-MB), peak troponin and NT-proBNP were found to be higher; while hemoglobin values were found to be lower in CIN patients. Age, AF, HT, left ventricle ejection fraction, hemoglobin, peak CK-MB, peak troponin, NT-proBNP and PHR were independent risk factors according to regression analysis (P=0.001, P<0.001, P<0.001, P=0.046, P=0.001, P=0.001, P=0.010, P=0.009, P=0.007, P<0.001, respectively). The receiver operating characteristic showed that the optimal PHR value for estimating the CIN was 1.86, with 66.1% sensitivity and 63.9% specificity (area under the curve: 0.686; 95% CI: 0.647-0.724, P<0.001).
Conclusions: A relationship has been found between PHR and CIN. PHR may provide more benefits than conventional blood markers in reckoning CIN.

KEY WORDS: acute coronary syndrome, contrast-induced nephropathy, hemoglobin, platelet, platelet-hemoglobin ratio

INTRODUCTION

For a long time, it has been well known that early and rapid coronary angiography (CAG) and percutaneous coronary intervention (PCI) in patients with the acute coronary syndrome (ACS) reduce heart failure, decrease mortality rates and offer a much better long-term prognosis[1,2]. Due to these benefits, today the primary treatment strategy for patients with ACS is an invasive treatment, and the frequency of its application is increasing daily. With the rising number of angiographic procedures, the complications that develop due to these are also increasing. Contrast-induced nephropathy (CIN) is one of them and causes increased mortality and morbidity in these patients[3,4].

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Upon examining the literature, many whole blood data have been reviewed to evaluate the prognosis of cardiovascular diseases[5,6]. In studies assessing platelet counts, it has been observed that both poor cardiovascular outcomes and CIN are more common in patients with high platelet counts[7-10]. It has been stated that the more frequent presence of inflammation caused by increased platelet counts and increased platelet activation may be responsible for this situation[11,12]. Additionally, anemia was also found to be a risk factor in the development of CIN. In studies of CIN from the outset, having low hematocrit and hemoglobin values leads to poorer cardiac outcomes while significantly increasing the development of CIN[13]. Concomitant chronic disease anemia supports this theory, especially in individuals with chronic kidney disease. The primary pathology here seems to be direct contrast agent exposure, which creates an additional perfusion defect on top of local renal ischemia due to anemia. Again, increased inflammation with anemia also contributes to the development of CIN[13,14].

Platelet-hemoglobin ratio (PHR) is a new parameter with proven predictive value in heart failure (HF), coronary artery disease (CAD), PCI and other malignancies that have gained attention recently[15-17]. No studies, however, have investigated the relationship between PHR and CIN. Our study aimed to examine the relationship between PHR and the development of CIN in patients who presented with ACS and underwent PCI.

SUBJECTS AND METHODS

Population

The study was planned as a retrospective, single-center study. Included were 1513 patients who were admitted to the hospital due to ACS between August 2017 and October 2021. CAG and PCI were performed on all patients within 48 hours after admission. In all patients, the nephrotropic, water-soluble, low osmolar, nonionic contrast agent for angiographic procedures Iohexol (300 mg iodine/ml; 672 mosml/kg of water; Omnipaque; GE Healthcare Inc., USA) was used. All patients were given dual antiplatelet therapy (300 mg ASA+ 600 mg Clopidogrel/180 mg Ticagrelor) and were anticoagulated with heparin infusion following indication. Intravenous infusion of saline was given according to the recommended guidelines for the prevention of CIN. In patients with preserved ejection fraction (EF), a dose of 1 ml/kg/hour was administered and 0.5 ml/kg/hour if the EF was lower, according to the decision of the following cardiologist depending on the clinical condition of the patient. During the percutaneous procedure, 70-100 IU/kg heparin was administered to the patients, with an additional dose of heparin administered by adjusting the activated clotting time to be kept above 250. GpIIb-IIIa inhibitor [Tirofiban (Aggribloc) 5 mg/100 mL; Nic-Nicolas Piramal India Ltd, Delhi, India] was administered as recommended by ad-hoc guidelines by the operator's decision, influenced by the CAG result. The relevant physicians performed PCI and CAG procedures following the guidelines[18,19]. All demographic data, medical history, laboratory and echocardiographic data were obtained from the hospital's electronic clinical management system. Blood samples were obtained from the peripheral venous route during emergency service admission. Patients with no platelet and hemoglobin data, cardiogenic shock, active infection, chronic nephrotoxic drug use history and end-stage renal disease were excluded.

Blood analysis

Blood samples were obtained from a peripheral vein at the patient's first visit and 48-72 hours after the procedure. Automatic hematology analyzers (Symex XN-550 analyzer, Symex, Kobe, Japan) were used to measure whole blood parameters, biochemistry devices performed biochemical analyses (Beckman Coulter Inc., Brea, New York, USA), and recorded data were obtained from the hospital electronic database. PHR was obtained by dividing the platelet count (10^9/L) in whole blood analysis by the hemoglobin count (g/L) (PHR = Platelet count/hemoglobin count)[18]. (When calculating PHR, 10^9/L is used for platelet and g/L for hemoglobin).

Echocardiographic examination

The echocardiographic assessment was performed using a VIVID 7 Dimension Cardiovascular Ultrasound System (Vingmed-General Electric, Horten, Norway) with a 3.5 MHz transducer. An echocardiographic examination was conducted in the left lateral decubitus position. Parasternal long- and short-axis and apical views were used as standard imaging windows. The ejection fraction was calculated using the modified Simpson method. An experienced cardiologist performed all echocardiographic examinations.

Definitions

CIN was defined as a ≥25% increase in baseline creatinine or an increase in creatinine of more than ≥ 0.5mg/dl 48-72 hours after PCI[19]. Patients with a diagnosis of hypertension (HT) were defined as using antihypertensives or by meeting the definitions specified by the European Society of Cardiology (ESC) guidelines[20]. Diabetes mellitus (DM) was defined as patients taking oral antidiabetic medications, using insulin and complying with the definitions of the American Diabetes Association[21]. Hyperlipidemia (HL) was defined as meeting the definitions specified by the ESC guidelines[22]. High PHR and low PHR groups were determined according to the values below

Table 1: Baseline characteristics, laboratory results of all study patients, and patients with and without CIN.

Demographics	Total study population n=1513	Non-CIN group n=1248	CIN group n=265	*P*
Age, years	61.3±13	60±12.1	68±14.8	<0.001
Male gender, n (%)	1083 (71.6)	931 (74.6)	152 (57.4)	<0.001
Atrial fibrillation, n(%)	202 (13.4)	107 (8.6)	95 (35.8)	<0.001
Diabetes mellitus, n (%)	568 (37.5)	402 (32.3)	166 (62.9)	<0.001
Hypertension, n (%)	776 (51.4)	606 (48.7)	170 (64.2)	<0.001
Hyperlipidemia, n (%)	932 (61.6)	756 (60.6)	176 (66.4)	0.043
CAD, n(%)	593 (39.3)	481 (38.6)	112 (42.7)	0.121
HF, n (%)	1138 (75.2)	923 (74.0)	215 (81.1)	0.008
Smoking, n (%)	628 (41.6)	546 (43.9)	82 (32.1)	<0.001
BMI, kg/m^2	27.7±5.1	27.8±5.1	27.6±5.6	0.603
On admission, clinical characteristics				
Systolic blood pressure, mm/Hg	136.4±38.6	136.4±40.5	136.6±28.9	0.934
Heart rate per minute	80.2±19.8	79.8±19.4	82.5±21.8	0.044
Left-ventricular ejection fraction (%)	42.6±10.4	43.0±10.3	40.4±10.6	<0.001
MI type (%)				
Anterior MI (%)	398 (26.3)	282 (22.6)	116 (43.8)	
Inferior MI (%)	496 (32.8)	440 (35.3)	56 (21.1)	<0.001
NSTEMI (%)	619 (40.9)	526 (42.1)	93 (35.1)	
Laboratory results				
Hemoglobin, g/L	138.2±24.6	140.1±23.7	129.6±27.1	<0.001
White blood cell count, 10^9/L	10.6±5.3	10.5±4.9	10.7±5.6	0.636
Platelet count, cells/ 10^9/L	261.4±85.1	261.3±84.2	261.6±88.8	0.962
Admission blood glucose, mg/dL	168.3±88.8	164.1±86.4	187.8±96.9	<0.001
Baseline creatinine, mg/dL	1.2±0.9	1.2±0.9	1.3±1.1	0.272
Peak creatinine, mg/dL	1.4±1.1	1.4±1.1	1.8±1.2	<0.001
Peak creatine kinase–myocardial band, ng/mL	78.2±197.6	70.5±199.3	114.3±185.4	0.001
Peak troponin, ng/l	10688±5538	10498±5541	11581±5446	0.004
NT-proBNP, pg/dL	2156±2985	2781±78.7	3714±228.2	<0.001
Total cholesterol, mg/dL	183.3±114.9	185.6±124.4	171.8±42.4	0.156
TG, mg/dL	174.5±172.3	178.6±185.2	154.3±84.1	0.052
HDL, mg/dL	39.7±13.8	39.5±13.1	40.51±17.3	0.396
LDL, mg/dL	125.3±36.1	125.9±36.5	122.2±34.0	0.122
Platelet-Hemoglobin Ratio	1.98±0.96	1.95±0.96	2.13±0.95	0.005
Angiographic and clinical data				
Multi-vessel stenosis (> 50%), n (%)	430 (28.4)	363 (29.1)	67 (25.3)	0.120
LAD of the infarct-related artery, n (%)	751 (49.6)	586 (47.0)	165 (62.3)	<0.001
Contrast volume, mL	275.2±160.2	275.1±160.5	275.5±159.1	0.966
Need for dialysis, n(%)	31 (2.0)	0 (0)	31 (11.7)	<0.001
Length of hospital stay, days	6.9±5.0	6.5±4.9	8.9±4.6	<0.001
In-hospital mortality	60 (4.0)	35 (2.8)	25 (9.4)	<0.001

CIN: contrast-induced nephropathy; CAD: coronary artery disease; HF: heart failure; BMI: body mass index; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; NT-proBNP: N-terminal prohormone brain natriuretic peptide; TG: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LAD: left anterior descending artery

and above the cut-off value found from the receiver operating characteristics (ROC) analysis.

Ethics approval

Ethics committee approval was received from the ethics committee of the University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey (Date number:18.04.2022, number:135/07).

Statistical analysis

The data were analyzed with the SPSS 23.0 statistical program (SPSS Inc., NY USA). Continuous variables are given as mean ± standard deviation, and categorical data are shared percentages and numbers (n). The student's t-test was used for normally distributed data, and the Mann-Whitney U test was used for data that did not show normal distribution. Categorical data were compared with the chi-square test. Univariate regression analysis was performed to find predictive factors for the development of CIN. Multivariate regression analysis was applied to the significant parameters in the univariate test, and independent risk factors for the development of CIN were determined. ROC analysis was used to estimate the optimal cut-off value of PHR in indicating CIN. Sensitivity, specificity and area under the curve (AUC) were calculated. A 2-sided $P<0.05$ was considered as significant.

RESULTS

One thousand five hundred thirteen ACS patients were included in the study. The mean age of the patients was 61.3±13 years, with most of them being male (n=1083; 71.6%). CIN developed in 265 (17.5%) patients. The patients who developed CIN were of advanced age (68±14.8 years) and consisted mainly of males (n=152; 57.4%). Atrial fibrillation (AF), DM, HT, HL and HF were found to be more common in patients who developed CIN (*P*<0.001, *P*<0.001, *P*<0.001, *P*=0.043, *P*=0.008, respectively). Systolic blood pressure does not differ between patients with and without CIN (136.4±40.5 mmHg vs. 136.6±28.9 mmHg, *P*=0.934). However, heart rates were higher in patients who developed CIN (79.8±19.4 bpm vs. 82.5±21.8 bpm, *P*=0.044). Again, patients who developed CIN had lower EF (43±10.3% vs. 40.4±10.6%, *P*<0.001). While the development of CIN was detected mostly in patients with anterior myocardial infarction (MI), the group with the lowest development of CIN was found to be patients with inferior MI (282 (22.6%) vs. 116 (43.8%), 440 (35.3%) vs. 56 (21.1%)), *P*<0.001). The development of CIN was found to be significantly higher in patients with left anterior descending (LAD) being infarct-related artery (586 (47%) vs. 165 (62.3%), *P*<0.001).

Glucose, peak creatinine, peak creatinine kinase–myocardial band (CK-MB), peak troponin, N-terminal proBNP (NT-proBNP) and PHR values were significantly higher in the group with CIN (*P*<0.001, *P*<0.001, *P*=0.001, *P*=0.004, *P*<0.001, *P*=0.005, respectively). Conversely, hemoglobin levels were lower in the group with CIN (140.1±23.7 vs. 129.6±27.1, *P*<0.001). All other demographic, clinical and laboratory findings are shown in Table 1.

According to univariable regression analysis, age, male gender, AF, DM, HT, HL, HF, left ventricular ejection fraction (LVEF), hemoglobin, blood glucose, peak CK-MB, peak troponin, NT-proBNP, LAD being the infarct-related artery, and PHR were found to be significant predictor factors for the development of CIN. When these predictor factors were included in the multivariable regression analysis, age, AF, HT, HL, LVEF, hemoglobin, peak CK-MB, peak troponin, NT-proBNP, LAD being the infarct-related artery, and higher PHR were found to be additional independent risk factors (*P*=0.001, *P*<0.001, *P*<0.001, *P*=0.046, *P*=0.001, *P*=0.001, *P*=0.010, *P*=0.009, *P*=0.007, *P*<0.001, *P*=0.001, respectively) (Table 2).

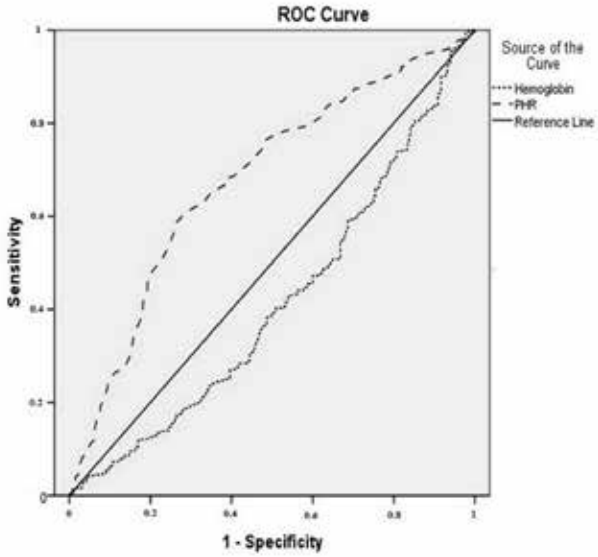

Figure 1: Receiver operating characteristics (ROC) curve for platelet-hemoglobin ratio (PHR) and hemoglobin.

When patients are grouped as low PHR and high PHR according to the cut-off value of PHR, CIN development and need for dialysis were higher

Table 2: Univariate and multivariate analyses for the predictor of CIN

Risk factors	Univariate analysis OR (95% CI)	*P*	Multivariate analysis OR (95% CI)	*P*
Age	1.050(1.039-1.062)	<0.001	1.025(1.011-1.039)	0.001
Male gender	2.183(1.659-2.874)	<0.001	1.285(0.901-1.831)	0.166
Atrial fibrillation	5.959(4.328-8.205)	<0.001	5.600(3.881-8.080)	<0.001
Diabetes mellitus	3.548(2.691-4.778)	<0.001	3.432(2.403-4.904)	<0.001
Hypertension	1.887(1.434-2.483)	<0.001	1.244(0.871-1.777)	0.230
Hyperlipidemia	1.287(0.974-1.701)	0.076	1.386(1.006-1.910)	0.046
Heart failure	1.514(1.086-2.112)	0.015	1.121(0.661-1.900)	0.672
Left-ventricular ejection fraction	0.975(0.963-0.988)	<0.001	0.987(0.967-1.008)	0.001
Hemoglobin	0.793(0.746-0.843)	<0.001	0.846(0.770-0.930)	0.001
Admission blood glucose	1.003(1.001-1.004)	<0.001	0.999(0.997-1.000)	0.111
Peak creatine kinase–myocardial band	1.001(1.000-1.001)	0.008	1.001(1.001-1.002)	0.010
Peak troponin	1.002(1.001-1.004)	0.004	1.001(1.000-1.001)	0.009
NT-proBNP	1.001(1.000-1.001)	<0.001	1.001(1.000-1.001)	0.007
LAD of the infarct-related artery	1.864(1.420-2.447)	<0.001	1.872(1.358-2.580)	<0.001
Platelet-Hemoglobin Ratio	1.016(1.004-1.029)	0.008	1.011(1.003-1.021)	0.001

CIN: contrast-induced nephropathy; NT-proBNP: N-terminal prohormone brain natriuretic peptide; LAD: left anterior descending artery

Table 3: Baseline characteristics, laboratory results of low PHR (<1.86) and high PHR (>1.86) groups.

Variables	Low PHR group (1.86>PHR), n=772	High PHR group (1.86<PHR), n=741	CIN group n=265
Demographics			
Age, years	60.91±12.2	61.8±13.8	0.204
Male gender, n (%)	445 (57.6)	638 (86.1)	<0.001
Atrial fibrillation, n(%)	82 (10.6)	120 (16.2)	<0.001
Diabetes mellitus, n (%)	261 (33.8)	307 (41.4)	0.001
Hypertension, n (%)	335 (43.4)	441 (59.5)	<0.001
Hyperlipidemia, n (%)	469 (60.8)	463 (62.5)	0.278
CAD, n(%)	299 (38.7)	294 (39.7)	0.519
HF, n (%)	583 (75.6)	555 (74.9)	0.192
Smoking, n (%)	346 (44.8)	282 (38.1)	0.004
BMI, kg/m^2	27.8±5.1	27.7±5.2	0.730
CIN, n(%)	103 (13.3)	162 (21.9)	<0.001
On admission, clinical characteristics			
Systolic blood pressure, mm/Hg	137.6±43.5	136.1±32.7	0.431
Heart rate per minute	78.19±19.5	82.6±19.9	<0.001
Left-ventricular ejection fraction (%)	42.4±10.3	42.7±10.6	0.685
Laboratory results			
Hemoglobin, g/L	147.1±22.5	131.8±21.2	<0.001
White blood cell count, $10^9/L$	10.4±4.8	10.7±5.2	0.301
Platelet count, cells/ $10^9/L$	206.9±43.5	305.2±64.9	<0.001
Admission blood glucose, mg/dL	167.6±90.2	169.3±88.6	0.719
Baseline creatinine, mg/dL	1.13±0.7	1.27±1.1	0.001
Peak creatinine, mg/dL	1.36±0.78	1.56±1.22	<0.001
Peak creatine kinase–myocardial band, ng/mL	78.3±173.7	77.4±221.6	0.936
Peak troponin, ng/l	10729.2±5523.1	10562.5534.1	0.563
NT-proBNP, pg/dL	2112.9±2878.7	2219.5±3100.3	0.493
HbA1c, %	8.1±2.3	8.3±3.7	0.224
Total cholesterol, mg/dL	188.4±154.8	179.4±47.5	0.225
TG, mg/dL	182.9±206.8	179.4±47.6	0.123
HDL, mg/dL	39.5±15.0	39.9±12.6	0.588
LDL, mg/dL	124.5±37.8	126.4±34.7	0.334
Platelet-Hemoglobin Ratio	1.41±0.28	2.35±0.52	<0.001
Angiographic and clinical data			
Multi-vessel stenosis (> 50%), n (%)	214 (27.7)	216 (29.1)	0.158
LAD of the infarct-related artery, n (%)	373 (48.3)	378 (52.4)	0.202
Contrast volume, mL	276.8±162.4	270.7±154.3	0.460
Need for dialysis, n(%)	10 (1.3)	21 (2.8)	0.027
Length of hospital stay, days	7.0±5.0	6.6±4.8	0.156
In-hospital mortality	34 (4.4)	26 (3.5)	0.343

PHR: platelet-hemoglobin ratio; CAD: coronary artery disease; HF: heart failure; CIN: contrast-induced nephropathy; BMI: body mass index; HbA1c: glycosylated hemoglobin; NT-proBNP: N-terminal brain natriuretic peptide; TG: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LAD: left anterior descending artery

in patients with high PHR (n=1037; 13.3% vs. n=162; 21%, *P*<0.001 and n=10; 1.3% vs. n=21; 2.8%, *P*=0.027). In patients of the group with high PHR, it was again determined that male gender and chronic diseases such as AF, DM and HT were more common. Other findings are summarized in Table 3.

The AUC of the PHR for the development of the CIN was 0.686 (95% CI: 0.647-0.724, *P*<0.001) in ROC analysis. The best cutoff value for the PHR was >1.86 for the prediction of CIN (sensitivity: 66.1%, specificity: 63.9%) (Table 4, Figure1).

DISCUSSION

In this study, we examined the ability of PHR value at presentation in the emergency department to predict CIN in ACS patients who underwent PCI. The primary result of our study was that the incidence of CIN was found to be higher in patients with high PHR values (1.95±0.96 vs. 2.13±0.95, *P*=0.005). This result is consistent with the results of other studies in the literature on ACS and other cardiac diseases and their poor outcomes[18,23,24]. In this patient group, we additionally found that advanced age, HT, HL, AF, low LVEF, low hemoglobin levels, elevated troponin, CK-MB, NT-proBNP levels, and LAD being the infarct-related vessel were associated with CIN.

CIN refers to a pathological condition in which renal damage occurs by different mechanisms, usually after using iodine-based contrast agents that significantly increase the sensitivity of medical

Table 4: Receiver operating characteristics analysis results for PHR and hemoglobin.

Risk factor	The area under the curve (95%)	Cut-Off	*P*	Sensitivity (%)	Specificity (%)
PHR	0.686 (0.647-0.724)	1.86	<0.001	66.1	63.9
Hemoglobin	0.321(0.286-0.357)	134.5	<0.001	55.1	65.2

PHR: platelet-hemoglobin ratio

imaging[25]. Today, with the expansion of the field of interventional treatment, the frequent use of contrast agents has increased the incidence of CIN. CIN has become the third most common cause of acute renal failure, as well as a common cause of hospital-acquired renal injury[26,27]. Although the incidence of CIN remains uncertain due to differing diagnostic criteria in studies, it is understood that the rate of CIN development in patients with ACS is higher than the average population[28]. The incidence of CIN development in our study was 17.5%, similar to other studies[29]. CIN is a severe complication in patients undergoing PCI. Increased incidence of CIN in patients undergoing PCI is associated with significant adverse clinical events such as prolonged hospital stay, renal failure, increased incidence of cardiovascular events, and high mortality[30-32]. In our study, we found that patients who developed CIN had higher hospital stays and in-hospital mortality, similar to previous studies. While there is no effective treatment for CIN, it is a condition that seriously threatens the patient's prognosis. Therefore, early recognition of CIN and, more importantly, good prediction is essential for the prognosis of patients undergoing PCI[29,33]. To our knowledge, there is no study in the literature evaluating the relationship between PHR and CIN. Our study is the first to assess the relationship between PHR and CIN. Risk factors proven to be associated with the development of CIN after PCI include advanced age, chronic kidney disease, DM, heart failure, anemia, and large amounts of contrast material[29,34,35]. In this study, we found that the basal creatinine levels and the amount of contrast agent used in patients who developed CIN were similar to those who did not. We also found that HT, which had conflicting results in its relationship with CIN in previous studies, is associated with the development of CIN in the population of our study[25,29,36]. Our research also observed that high NT-proBNP, peak troponin and peak CK-MB levels were associated with CIN. In the study conducted by Kurtul *et al* on 436 patients with ACS, the relationship between NT-proBNP, peak troponin, peak CK-MB levels and CIN was evaluated. The study found that high NT-proBNP and peak troponin levels offered a predictive value for CIN, while peak CK-MB levels were not associated with CIN development, contrary to our study[37]. Here, increased NT-proBNP, troponin and CK-MB reflect MI after ACS. The high levels of these markers also indicate the size of the affected myocardial tissue after ACS. The more myocardial tissue affected, the more the EF will decrease, advancing the severity of heart failure. More severe heart failure leads to greater end-organ damage. For this reason, it is significant and logical that NT-proBNP, troponin and CK-MB values are higher in patients who develop CIN. Additionally, myocardial-derived proteins such as CK-MB and troponin may also contribute to the development of CIN due to their direct nephrotoxic effects, which may have contributed to the higher incidence of CIN in these patients[38,39].

In the pathophysiology of CIN, many mechanisms exist, such as direct damage by the contrast to renal tubular epithelial cells, renal hemodynamic instability, renal ischemia, and oxidative stress caused by reactive oxygen radicals. However, recent studies have proven that increased inflammation, cellular toxicity, and apoptosis also play a role in the development of CIN[25,40]. Considering the pathophysiological mechanisms, we believed there may be a significant relationship between PHR and CIN. Based on the previous data, renal ischemia is the result of anemia, and the increased inflammatory and thrombotic response is due to high platelet levels associated with CIN. Indeed, in our study, we found that patients with ACS and high PHR have a higher chance of developing CIN after PCI.

In recent years, PHR has emerged as a new prognostic predictor for cardiovascular diseases. Zheng *et al* showed that a high PHR rate is an independent prognostic marker in patients with CAD who underwent PCI, and functions as a better blood parameter than platelet count and hemoglobin levels alone[17]. Likewise, Bao *et al* showed that high PHR was an independent predictor of long-term all-cause mortality in patients with HF[15]. In the recent past, the relationship between CIN and parameters such as neutrophil-lymphocyte ratio and systemic-immune inflammatory index, which can be calculated with whole blood data, were evaluated and shown to have prognostic importance[41,32]. The presence of anemia increases platelet count and

contributes to the development of CIN with direct renal ischemia[15]. PHR is thus valuable unlike other inflammatory parameters, because it is indirectly associated with renal ischemia and increased inflammation. It can show the development of reactive thrombocytosis due to anemia and CIN together. However, PHR includes two parameters. In our study, when the platelet or hemoglobin levels were examined alone, there was no difference between platelet counts, and any predictive value cannot be assessed. The ROC analysis showed that the AUC value of hemoglobin is relatively low compared to PHR. This result demonstrates that PHR is a much more effective and accurate predictor of CIN development than platelet and hemoglobin values alone. Our study showed the relationship between CIN and high PHR in a group of patients with ACS that had not been previously investigated. We believe that this newfound result will contribute to the literature.

Limitations

Our study has some limitations. First of all, our study is a single-center and retrospective study. It is known that renal damage can occur in ACS without the administration of contrast material. Therefore, another limitation of our study is that we used the in-hospital pre-procedural creatinine level as the baseline value, which may not have represented the patients' actual baseline serum creatinine level. The preprocedural hemodynamic parameters during emergency admission of the patients were examined. However, we do not have any data on hemodynamic parameters (hypotension, bradycardia, etc.) during the PCI.

CONCLUSION

Our study indicates that high PHR is a new, independent predictor of CIN in patients with ACS undergoing PCI. This may be useful for the risk stratification of CIN development. However, prospective multicenter studies are needed to provide more substantial evidence to confirm our finding.

ACKNOWLEDGMENT

There is no specific funding obtained.

Author contribution: Nail Burak Ozbeyaz: study design, acquisition of data, analysis and interpretation of data, drafting of manuscript, statistical analysis; Gokhan Gokalp: acquisition of data, analysis and interpretation of data; Engin Algul and Haluk Furkan Sahan: critical revision.

Conflict of interest: All authors declare that they do not have any conflicts of interest.

Disclosure statement: The authors have no relevant financial or non-financial interests to disclose.

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Original Article

Is a single anterior and single lateral portal sufficient for the arthroscopic treatment of the combination of supraspinatus tear and SLAP lesion?

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Kuwait Medical Journal 2024; 56 (4): 325 - 329

ABSTRACT

Objectives: We investigated to compare anterior and lateral single portal application with standard techniques in the arthroscopic treatment of superior labrum anterior-posterior (SLAP) lesions and supraspinatus tears.
Design: A retrospective case-control study
Setting: Usak University Medical Faculty, Usak, Turkey
Subjects: Two hundred seventy-eight patients with arthroscopic SLAP lesions and supraspinatus tear repair were analyzed. Forty-one patients who met the criteria were included in the study.
Interventions: The patients were divided into two groups: a single working portal (n=21) and a double working portal (n=17), according to the operation technique used.
Main outcome measures: Pain and functional outcomes were evaluated with the Visual Analog Scale (VAS) and Constant Murley Scale (CMS), and time of operation, and return to daily routine times were evaluated.
Results: When the two groups were compared statistically in terms of VAS and CMS values, there was no significant difference (pre-operative: *P*=0.336, 0.926 respectively; at the 6th week after the operation: *P*=0.735, 0.750 respectively; at 1-year postoperatively: *P*=0.399, 0.689, respectively). A shortening of the operation time was observed in the first group (*P*=0.027), and no difference was found in the other parameters in the short and long term.
Conclusions: The use of isolated anterior and isolated lateral portals in the surgical treatment of supraspinatus and SLAP lesion coexistence will shorten the operation time, prevent the formation of additional scar tissue, and reduce the risk of neurovascular injury due to additional portal openings.

KEYWORDS: auxiliary portal, single portal, slap, supraspinatus

INTRODUCTION

Rotator cuff injuries are common shoulder pathologies. The incidence of injury increases with age, increasing from 9.7% under age 20 to 62% over age 80[1]. The long head of biceps humeri pathologies often accompany rotator cuff injuries, but the rate of association is unknown[2]. Today, the treatment of shoulder pathologies is usually performed arthroscopically. With the widespread use of arthroscopy, various auxiliary portals have been identified[3]. Accurate recognition of the main and auxiliary portals and opening them from the appropriate areas provide convenience during the operation. Although the increase in the number of portals makes the operation relatively easy, it causes the risk of neurovascular injury and cosmetic impairment due to additional incisions[4-6].

As a standard, the anterior double portal technique is used in the treatment of superior labrum anterior-posterior (SLAP) lesions, and lateral 2 or 3 portal techniques are used in rotator cuff repairs[7]. Repairing from a single portal has been described as an option in the treatment of various isolated shoulder pathologies, but its application has not been defined in the combination of SLAP and supraspinatus[8-13].

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Figure 1: Portals

Our study aims to compare the anterior and lateral single portal application with the standard technique in the arthroscopic treatment of SLAP lesions and supraspinatus tears. We hypothesized that the described technique might be effective in the treatment.

SUBJECTS AND METHODS

After the approval of the ethics committee, 278 patients who underwent arthroscopic intervention for various shoulder pathologies by the senior author between 2015-2019 in our clinic were retrospectively reviewed. Patients with arthroscopically performed SLAP lesions and supraspinatus tear repair were included in the study.

Patients who underwent isolated supraspinatus and SLAP lesion repair, Bankart repair, subscapularis repair and biceps tenotomy, patients who were operated on for massive cuff rupture, patients who only underwent debridement of the SLAP lesion, patients who did not undergo acromioplasty, patients who developed adhesive capsulitis in the postoperative period, those who do not attend their routine follow-ups and patients who developed re-rupture formed the study exclusion criteria. Accordingly, 62 patients with isolated supraspinatus repair (22%), 18 patients with isolated SLAP repair (6%), 13 patients with Bankart repair (5%), 22 patients with subscapularis repair (8%), 37 patients with biceps tenotomy (13%), eight patients with massive cuff rupture (3%), 43 patients who underwent SLAP debridement (15%), 18 patients who did not undergo acromioplasty (6%), six patients who developed adhesive capsulitis (2%), four patients who did not follow up (1%), and six patients (2%) who developed supraspinatus tendon re-rupture were excluded from the study.

Forty-one patients (15%) included in the study were divided into two groups according to the operation technique. There were 24 patients in the first group using isolated anterior and isolated lateral portals, and 17 patients in the second group, in which auxiliary portals were used in addition to the anterior and lateral portals.

Operation times, return to the daily routine, and demographic characteristics were recorded. Pain and functional outcomes were evaluated with the Visual Analog Scale (VAS) and Constant Murley Scale (CMS) before the operation, in the 6th week and 1st year after the operation.

In the first group, after SLAP repair, the anterior portal was pulled backward and advanced to the subacromial region under the deltoid and used as an aid to the lateral portal for supraspinatus repair (Fig 1). In the second group, auxiliary portals opened in addition to these portals were used. All patients in the study underwent SLAP lesion repair with a 3.5 mm anchor between 12 and 1 o'clock and a double row technical supraspinatus tear repair with the help of a 5 mm anchor and 4.5 mm knotless anchor (Fig 2). All operations were performed in the lateral decubitus position.

Standard protocol physical therapy was applied to all patients after surgery; elbow, wrist and hand movements were started from the first day after the surgery, passive range of motion exercises were

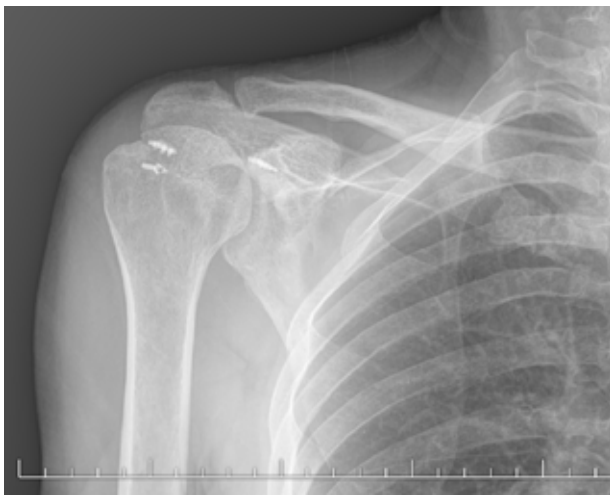

Figure 2: Case example

given until the 4th week, active assistive exercise program after the 4th week, and strengthening exercises were given from the 6th to the 12th week.

SPSS v.24 Mann-Whitney-U analysis was used for statistical analysis (IBM Corp., Armonk, New York, USA). A *P*-value less than 0.05 was considered significant.

RESULTS

Twenty-nine (71%) of the patients were female and their mean age was 52.3±11.4 (38-66) years. The mean age of men was 54.6±10.3 (44-66) years. Thirty-two (78%) of the injuries were in the right shoulder. All patients in the study were treated with arthroscopic supraspinatus and SLAP repair by the senior author.

Patients (n=6) who developed re-rupture in the supraspinatus tendon were three in both groups.

The mean pre-operative VAS and CMS values were 7.125±1.42 / 35.37±11.68 in the first group, in the second group in which the additional auxiliary portal was used: 7.53±1.54 / 34.53±10.18 (*P*=0.336, 0.926 respectively).

The mean VAS and CMS values at the 6th week after the operation were: 2.75±1.45 / 65.71±11.47 in the first group and 2.94±1.67 / 68.76±7.38 in the second group (*P*=0.735, 0.750 respectively).

The mean VAS and CMS values at 1-year postoperatively were 0.63±0.77 / 85.13±6.27 in group 1 and 0.41±0.62 / 84.76±7.16 in group 2 (*P*=0.399, 0.689 respectively; Table 1). Good to excellent functional and clinical results were obtained in both groups at one-year follow-up compared with preoperative values (*P*<0.001).

The mean time to return to the daily routine was 15.63±1.99 weeks in the first group and 15.71±1.79 weeks in the second group (*P*=0.883).

Table 1: Averages of VAS and CMS

VAS and CMS by the time	Group 1	Group 2	*P*-value
VAS pre-operatively	7.125±1.42	7.53±1.54	0.336
CMS pre-operatively	35.37±11.68	34.53±10.18	0.926
VAS 6 week	2.75±1.45	2.94±1.67	0.735
CMS 6 week	65.71±11.47	68.76±7.38	0.750
VAS 1 year	0.63±0.77	0.41±0.62	0.399
CMS 1 year	85.13±6.27	84.76±7.16	0.689

VAS: Visual Analog Scale; CMS: Constant Murley Scale

The mean operation time was 45.92±5.25 minutes in the first group in which isolated anterior and isolated lateral portals were used, and 53.53±11.24 minutes in the second group in which the additional auxiliary portals were used (*P*=0.027; Table 2).

Table 2: Time to return to the daily routine and operation time

Return to the daily routine and operation time	Group 1	Group 2	*P*-values
Time to return to the daily routine (week)	15.63±1.99	15.71±1.79	0.883
Operation time (minute)	45.92± 5.25	53.53±11.24	0.027

DISCUSSION

Shoulder arthroscopy is widely used in the treatment of shoulder pathologies today. In the study in which isolated anterior and isolated lateral portal and standard techniques were compared in the repair of SLAP lesion and supraspinatus tear, a statistically significant shortening of the operation time was observed in the 1st group (*P*=0.027). However, no difference was found in functional and clinical outcomes in the short and long term (*P*=0.399-0.750).

Auxiliary portals are used to support basic portals in reaching and repairing various pathologies. The biggest difficulty encountered in repairs made with a missing portal is that the ropes coming out of the anchor cause confusion within the joint. In repairs made with a single portal, re-taking the threads of other colors from the joint to the portal after the suture has passed through the tissue helps to prevent knot confusion. In this study, the isolated anterior portal was used in SLAP lesion repair, but while supraspinatus repair was performed, the anterior portal was transferred to the subacromial region as a subdeltoid and used as an aid. In the supraspinatus tear repair with double-row repair, a threadless anchor was used for lateral tension, while the other threads were shifted to the anterior portal to prevent suture confusion. Kim *et al* mentioned in their study that the ropes can get tangled[13].

In a study of 71 patients by Uzun *et al* in which they compared double and single portal in Bankart repair, they found no difference in postoperative clinical and functional results (P=0.083-0.318). However, they found a shortening in operation time in the group that underwent single portal technique compared to the other group (P<0.001)[8]. In the current study, which was consistent with this study, a shortening of the operation time was observed in the group in which isolated anterior and isolated lateral portals were used (P=0.027), and no significant difference was found in other evaluations.

Lavender *et al* described imaging with NanoScope (Arthrex, Naples, FL) and rotator cuff repair with the lateral portal in a technical note[12]. This study demonstrates that less invasive rotator cuff repair can be performed with a single lateral incision. The additional cost of the NanoScope, difficult viewing angles and reduced and/or difficult visualization have been identified as disadvantages of the technique. In this current study, the lateral portal was opened, and the anterior portal was used as an aid in supraspinatus repair. In the case of using a standard scope, it can be considered an advantage that there is no reduction in the viewing angle.

Another technical note describing spino-glenoid notch cyst and SLAP repair with a single working portal showed that the use of a single portal was cost and time-efficient[9]. The advantages of the described technique are the shorter operation time, iatrogenic rotator cuff injury and no need for a superior capsular incision. Similar to this study, it is seen that the operation time was shortened in our study (P=0.027).

Single portal repair of subscapularis tears has been described previously[10]. Difficulty in treating larger tendon tears, muscle atrophy, late repairs with retraction or fat infiltration, and the increased likelihood of entangled sutures with a single working portal have been noted as disadvantages of the technique. In the current study comparing the two techniques, massive or retracted rotator cuff tears and subscapularis tendon tears are among the exclusion criteria. Knot entanglement that developed due to the use of a single portal was prevented by taking the other threads back into the portal from within the joint after passing the knot through the tissue.

With each opened portal, the possibility of neurovascular injury increases, and additional incision scarring occurs. Considering this situation, it seems that it is more appropriate to apply the treatment process with the least possible portal. The main limitation of the study is its retrospective nature. We believe that more effective results will be obtained in the case of prospective randomized planning.

CONCLUSION

In the surgical treatment of supraspinatus and SLAP lesion coexistence, the use of isolated anterior and isolated lateral portals will shorten the operation time, avoid the formation of additional scar tissue and reduce the risk of neurovascular injuries due to additional portal opening. However, its long-term clinical and functional outcomes range from good to excellent, similar to the standard protocol.

ACKNOWLEDGMENT

The design of the analysis, the collection of data, and the writing of the article were carried out by the corresponding author. The co-author performed the manuscript analysis and statistical analysis. The authors declare that there is no conflict of interest.

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Case Report

Strain echocardiography and cardiac MRI evaluation of a symptomatic myopericarditis after the Pfizer-BioNTech mRNA COVID-19 vaccine

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Kuwait Medical Journal 2024; 56 (4): 330 - 333

ABSTRACT

The COVID-19 pandemic and the accompanying new generation vaccines have entered our lives with many unknown effects. This is a case report of myopericarditis diagnosed with fever and chest pain 3 days after the 2nd dose of Pfizer-BioNTech COVID-19 mRNA vaccine in an 18-year-old man. The diagnosis was confirmed by cardiac MRI (CMR), but our study indicates that this diagnosis and follow-up could be made accurately with strain echocardiography (SE).

KEY WORDS: COVID-19 vaccine, myocarditis, pericarditis, strain echocardiography

INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes Coronavirus disease 2019 (COVID-19). While this disease was considered as a respiratory tract disease in the first days of pandemic, now we know that it can present with a wide variety of complications affecting other systems, including cardiovascular system[1].

After pandemic, the search for vaccines against the disease began and a significant decline in COVID-19 mortality occured after these COVID-19 vaccines[2].

Because both COVID-19 itself and mRNA vaccines are new developments and their spectrum of effects are unknown, some new questions regarding these are raised. There are some reports about the myocarditis related to different types of COVID-19 vaccines, but there is only limited data[3].

Here, we present a case of an adolescent who developed symptomatic myopericarditis after the Pfizer-BioNTech mRNA COVID-19 vaccine, and describe the diagnostic process and evaluation with Strain Echocardiography (SE) and Cardiac MRI (CMR).

CASE REPORT

An 18-year-old male patient suffered from persistent fever and chest pain for 3 days after the second dose of the Pfizer-BioNTech mRNA COVID-19 vaccine. His electrocardiograpy (ECG) and hemogram were normal. Peak cardiac troponin I (TI) and C-reactive protein were raised at 100.4 ng/L and 44.1 mg/L respectively.

There was minimal pericardial effusion on echocardiography with normal systolic and diastolic ventricular functions. COVID-19 PCR test, Epstein-Barr virus, Cytomegalovirus, Toxoplasma, Rubella, human immunodeficiency virus, Hepatitis C antibody, Hepatitis B surface antigen, Rubeola and Mumps serological tests were negative.

Diagnosis of myopericarditis was made based on troponin elevation and pericardial effusion. He was started on Metoprolol-perindopril-colchicine and non-steroidal anti-inflammatory agent.

The SE and CMR examinations were performed during the patient's first hospitalization and control SE was performed just before discharge.

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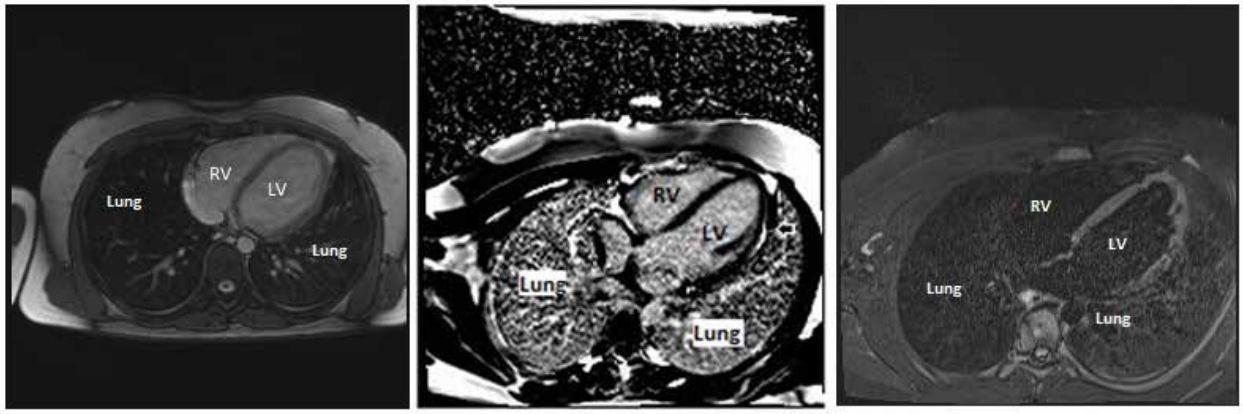

Figure 1: Myocardial edema and pericardial effusion were observed in cardiac MRI, consistent with acute myocarditis (LV: left-ventricule, RV: right ventricule, white arrow: pericardium)

CMR showed on T2-weighted imaging, increased bright signal intensity as myocardial edema and increased global early gadolinium enhancement ratio between myocardium and skeletal muscle as myocardial injury, especially on anterior wall, minimal pericardial effusion and depressed sytolic function with left ventricular ejection fraction of 44.3%. These findings were in favor of acute myopericarditis (Figure 1).

Unlike CMR, the left ventricular ejection fraction calculated by biplane Simpson's method was within normal limits. Although other transthoracic traditional-2D and Doppler echocardiographic findings (TE) were normal, depressed circumferential and longitudinal strain values were observed in the SE on anterior wall (Figure 2).

During the follow-up of the patient, TE findings were still normal, while a moderate increase in strain values was observed before discharge (Figure 3).

The patient was discharged on the 7th day with recovery after treatment. All examinations performed during the treatment process were performed with the informed consent of the patient.

DISCUSSION

Since some of the myopericarditis are asymptomatic, the incidence and prevalence of this disease is not known exactly[4]. However, it is suspected to be in the range of 1-10 cases per 100,000 persons and had a variable autopsy prevalence (2-42%)[4]. The causes of myocarditis include infectious and autoimmune etiologies[4].

In literature review of myocarditis cases after COVID-19 vaccination, nearly all of them had high TI, and most of them had abnormal ECG[1]. Only a half of them had abnormal echocardiographic findings[1]. There were late gadolinium enhancement and myocardial edema on CMR as a suggestion for myocarditis in these patients, as in other myocarditis cases[1]. Myopericarditis can be seen after many types and purposes of vaccines used today and is not specific to COVID-19 vaccines[3].

In the literature review of myopericarditis following COVID-19 vaccine, we noticed that males aged between 14-19 years old were affected, like our patient. All of the myopericarditis occured after second dose of vaccine[5], and approximately 60% of myocarditis

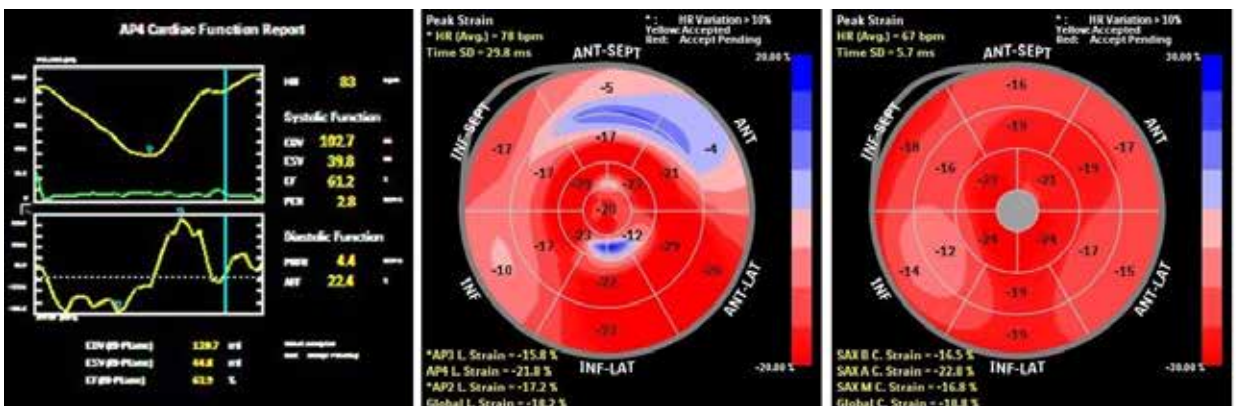

Figure 2: While the ejection fraction is normal in echocardiography, low global longitudinal and circumflexial strain were observed. In a patient with normal systolic function, this supports the diagnosis as much as cardiac MRI. The low strain value was observed that this strain reduction is especially in the anterior wall.

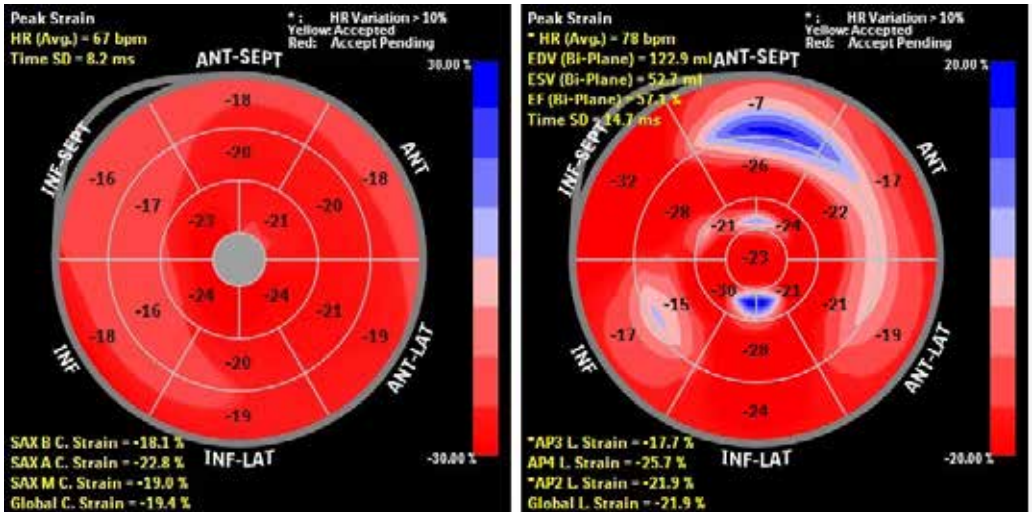

Figure 3: The improvement in the strain value of the patient before discharge is remarkable, the area with decreased in strain on the anterior wall was observed getting smaller.

developed especially after the Pfizer-BioNTech mRNA vaccine[5].

The mechanism of the COVID-19 vaccine associated myocarditis can be due to cross-reaction between the antibodies against SARS-CoV-2 spike glycoproteins and α-myosin[6].

As a noninvasive test, the diagnostic value of CMR in all myocarditis types is known[7]. Hence, in our case, CMR became the primary non-invasive test to assess the myocardial inflammation. However, it is more difficult to access with CMR than with the echocardiography, which is always in the hands of a cardiologist.

The reliability of various modes of echocardiography varies in the assessment of left ventricular size and function and hence newer investigations are proposed for the follow up of these functions affected by various cardiac pathologies[8]. SE allows us to assess the myocardial functions better. SE can evaluate the myocardial deformation and it reflects myocardial functions better than TE parameters. With the introduction of SE into clinical practice of cardiologists, we learned that, while TE assesses the myocardial functions indirectly, SE is more sensitive to detect early changes in myocardial functions[9]. SE had a better validation in different cardiac pathologies with better feasibility[10-14].

There are also data for the evaluation of myocarditis with SE in the current literature. In a study presented by Beata *et al*, they showed that myocarditis can be successfully diagnosed with SE[15]. Studies which compared the CMR and SE in the diagnosis and follow-up of myocarditis showed that both CMR and SE detected areas of myocardial inflammation with similar accuracy[16,17].

With the introduction of SE, it has been shown that it detects pathologies that cannot be detected in TE. The role of CMR in the diagnosis of myocarditis is known and it has been shown that there is a correlation with CMR and SE to detect myocardial involvement areas. According to these datas, SE can be an effective method to diagnose and follow up these patients, even if CMR is not available, or can be an alternative method if CMR is available too.

We also found similiar data in our case. Myocardial involvement of our patient was similar with SE when compared with CMR findings, while there was no significant pathology detected in TE evaluation. We detected an improvement in SE values before discharge in keeping with clinical recovery. The use of CMR in periodic follow up is more expensive than SE, which is a more practical, accessible, repeatable and cost-effective method for diagosis and on follow-up of these cases.

Management of these patients are similiar to non-vaccine myopericarditis. The treatment depends on the patient's clinical presentation, comorbidities and hemodynamic stability. Nonsteroidal anti-inflammatory drugs, steroids and colchicine are the main treatments for the control of the inflammatory process[3,4]. Beta-blockers and renin-angiotensin-aldosterone system inhibitors may be indicated to improve cardiac functions and to prevent arrhythmias. Severe myocardial dysfunction may need intensive care management with hemodynamic monitoring and mechanical support devices[3,4].

CONCLUSION

Our limited data from this case report of Pfizer-BioNTech mRNA COVID-19 vaccine induced myocarditis suggests that SE is as effective and a less

expensive method for the diagnosis and follow up as CMR. It would be beneficial for the cardiologists who perform the primary follow-up of these patients to know that it is possible with SE to support the diagnosis and follow-up of these patients, even if CMR is not available.

ACKNOWLEDGMENT

All authors declare that there is no conflict of interest and funding. Emre Ozdemir: data collection and writing; Banu Karaca: critical review and language editing. We acknowledge the contribution of Dr. Selin Ozdemir in the preparation of the manuscript.

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Case Report

Laryngeal adenoid cystic carcinoma treated by radiofrequency coblation assisted laryngectomy

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Kuwait Medical Journal 2024; 56 (4): 334 - 339

ABSTRACT

Laryngeal adenoid cystic carcinoma (LAdCC) is rare, and long-term prognosis is poor. We want to investigate an effective treatment for LAdCC. Here, we present two cases of LAdCC treated by radiofrequency coblation (RFC) assisted laryngectomy and update a systemic review. Working thickness of RFC plasma field is up to 200 μm thick, indicating an extra 200 μm deep tissue dissolving and removal as compared to conventional surgical resection. RFC-assisted laryngectomy might provide an additional safety dissection margin, which is particularly important for LAdCC because the tumor tends to infiltrate submucosal tissues. The neurovascular structures involved by tumor are easily identified and removed owing to a clear surgical field provided by efficient hemostatic control. This is essential because tumor perineural invasion is common; a clear surgical field might reduce the possibility of tumor remaining after surgery. In addition to fast tumor removal, less intra-operative complications and rapid post-operative recovery, RFC-assisted tumor-dissection might induce anti-tumor immunity providing additional therapeutic effect to destroy possible remaining cancer cells after surgery. Our study provides a promising treatment for LAdCC.

KEY WORDS: adenoid cystic carcinoma, larynx, radiofrequency coblation

INTRODUCTION

Laryngeal adenoid cystic carcinoma (LAdCC) originating from minor salivary glands is extremely rare, the overall incidence is about 0.005 per 100,000 population each year[1]. The carcinogenesis mechanism of LAdCC is not clear, and smoking is not a risk factor[2]. There is no significant sex disparities in the incidence of tumor[1,3].

Subglottis is the most common site of origin of LAdCC (59%), followed by supraglottis (32%) and glottis (10%); the difference in incidence are probably correlated with the different distribution-density of submucosal glands in these anatomical areas[2].

Clinical symptoms are associated with tumor size and location. Supraglottic AdCC may present with pharyngolaryngeal paresthesias, odynophagia and dysphagia accompanied by ear pain; glottic AdCC may have symptoms of hoarseness, dysphonia and dyspnea; while patients of subglottic AdCC may present with symptoms of dyspnea, stridor and airway obstruction[4-6].

Of a variety of clinical presentations, unexplained pharyngolaryngeal pain and or paresthesia are more likely the early signs of perineural involvement of LAdCC[7]. When there is suspicious discrepancy between the intensity of pain and the appearance of "look-like normal" on laryngoscopy, clinicians should be vigilant in the concern of submucosal LAdCC[2].

LAdCC is featured by slow submucosal growth at the beginning, local recurrences after initial treatment probably due to tumor perineural invasion and tumor remaining after surgery, and late hematogenous dissemination to distant organs, such as lungs, bone and brain. Long-term prognosis is poor[8].

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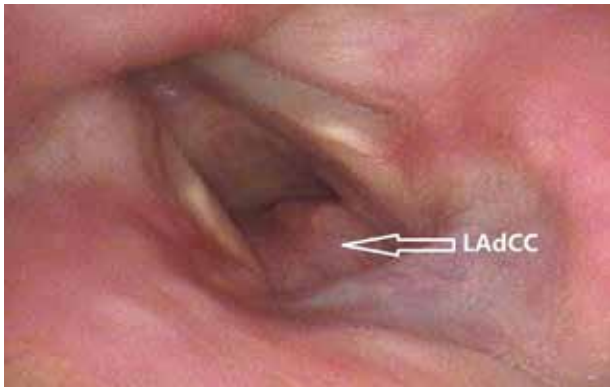

Fig. 1: Laryngoscopy of Case 1 in 2014. A tumor is in the left posterior para-median region of subglottic area partially blocking airway, the mobility of left true vocal cord is affected due to the oppression of the mass, the right true vocal cord is normal.

LAdCC represents a therapeutic challenge. Pharyngolaryngeal anatomy is complicated with many cranial nerves and blood vessels, bleeding is always a problem during manual cold steel dissection of larger tumor. Bleeding can blur the difference in appearance between normal and tumor tissue and make it difficult to identify and remove tumor completely. Minimizing bleeding is essential to provide a clear operative-field and decrease the possibility of tumor remaining after surgery[9].

Radiofrequency coblation (RFC) has many advantages, such as lack of charring with minimal or no damage to surrounding tissues, simultaneous hemostatic control and tumor-dissection. Effective hemostasis can improve visualization and differentiation between normal and tumor tissues. RFC-assisted surgery might also upregulate anti-tumor immunity. These assets make RFC an appropriate technique for resection of malignant tumors[10].

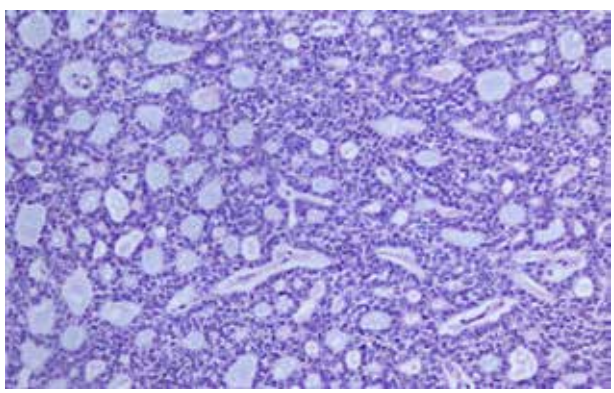

Fig. 2: Pathological diagnosis of case 1. The cancer cells are small and bland hyperchromatic with prominent nuclear-to-cytoplasmic ratio, the fenestrated cancer cells cluster together forming the pseudoglandular spaces which are filled with mucin and basement membrane-like material.

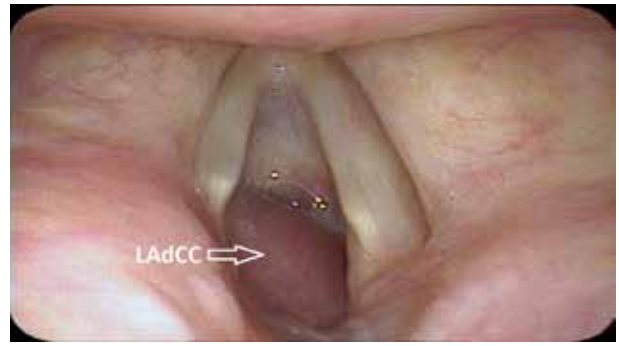

Fig. 3: Laryngoscopy of Case 1 in 2015. The posterior 2/3 of left vocal cord is involved by the tumor, and the left vocal cord is fixed at para-median position, the mobility of the right vocal cord is normal.

However, LAdCC treated by RFC-assisted laryngectomy has never been reported before. Here, we hope to share our experience in tumor-resection using RFC in two cases of LAdCC and present a systematic review. Our study is approved by Hospital Human Research Ethical Review Board with informed consents from participants.

CASE REPORT

Case 1

In August of 2014, a 60-year-old man was admitted to the hospital with a 1-year history of pharyngolaryngeal paresthesias, 20-day history of inspiratory dyspnea accompanied by hoarseness, dysphonia and pharyngolaryngeal pain. Laryngoscopy revealed a hemispherical smooth-surface mass in the left subglottic area, shown in Figure 1. After tracheostomy and biopsy, pathological diagnosis was AdCC, a predominant cribriform sub-phenotype with less than 30% of solid component, shown in Figure 2.

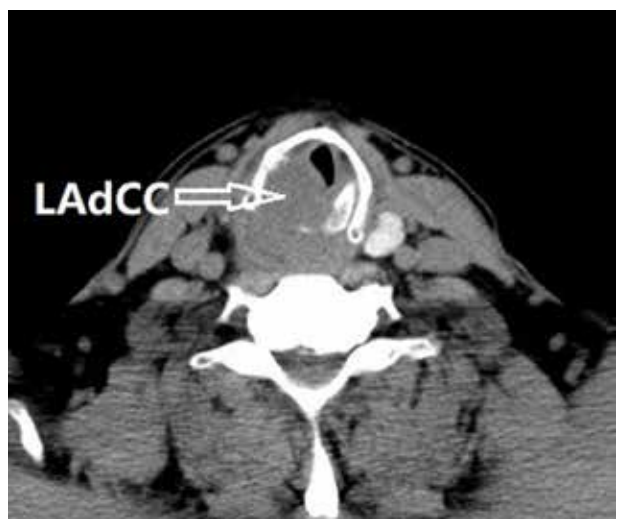

Fig. 4: CT scan of case 1. The subglottic tumor upward spreads to the left vocal cord, and inferiorly extends to cervical trachea to the level of the 7th cervical vertebra. The subglottic caliber is reduced by the space-occupying tumor.

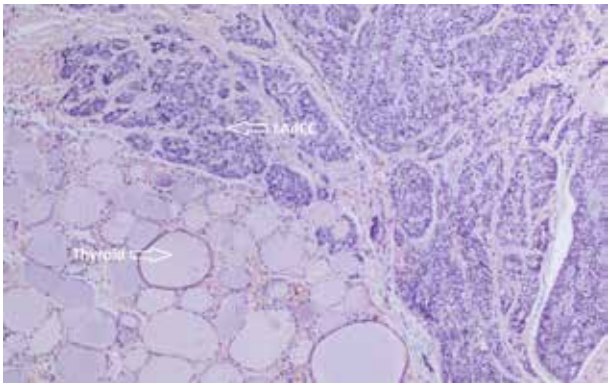

Fig. 5: Tumor invasion of thyroid gland in case 1. After laryngofissure a pink colored submucosal solid mass with intact surface is noticed in the left subglottic area, it semi-circumferentially occupies about 2/3 transverse section of the lumen. The tumor involves cricoid cartilage, the first cervical trachea, median cricothyroid ligament and front neck muscles, and invades thyroid gland.

Immunohistochemical study showed positive staining of P53, P63, SMA, CD117, CK (Pan), and Ki67 (+5%), and negative staining of CaLponin, EMA and GFAP. Immunohistochemical results supported the diagnosis of AdCC.

However, the patient refused next step therapy until he returned to our department asking for further treatment in February 2015. Laryngoscopy revealed that the subglottic mass had enlarged as compared to that shown in 2014, shown in Figure 3. Contrast-enhanced CT showed a hyper-accumulation of tracer predominantly in the left subglottic region, indicating a solid and inhomogeneous tumor, shown in Figure 4. There were a few palpable enlarged cervical lymph nodes on the left neck.

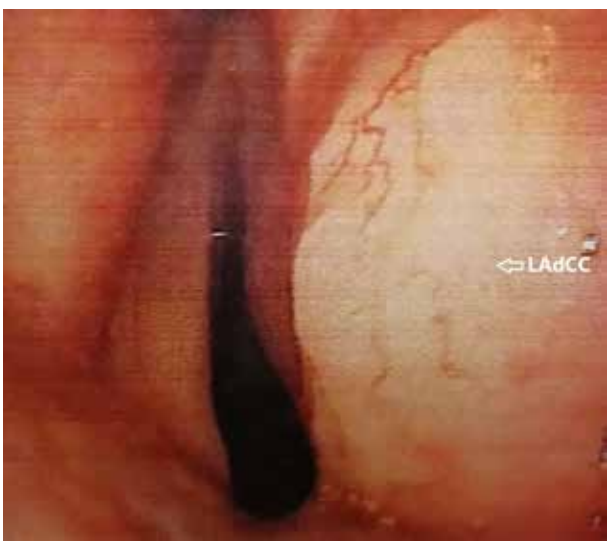

Fig. 6: Laryngoscopy of case 2. A huge mass is on the right aryepiglottic fold with protrusion of the right laryngeal ventricle and fullness of the right pyriform sinus. The right vocal cord and anterior commissure are swelling and partially over-lapped by the tumor. The right vocal cord is fixed at the paramedian position, the movement of the left vocal cord is also affected and limited. Airway is partially obstructed.

Case 1 underwent total laryngectomy, bilateral functional neck dissection plus en-bloc resection of thyroid gland because of tumor infiltration, shown in Figure 5. RFC was adopted in the surgery by using low-temperature radiofrequency and saline to create a plasma field. Radiofrequency energy excites electrolytes in normal saline, and these activated electrolyte particles acquire sufficient energy to split molecular bonds within tissues, causing the tissues to disintegrate and dissolve[11].

LAdCC can be resected accurately and completely owing to efficient hemostatic control. RFC was utilized to hopefully provide extra safety margins. The radiofrequency energy is reported to penetrate and remove surrounding tissues to a depth up to 200 μm[12]. After LAdCC was dissected by conventional surgery and safety margin specimen were obtained, RFC was adopted to vaporize suspected areas of tumor bed of potential residual cancer cells.

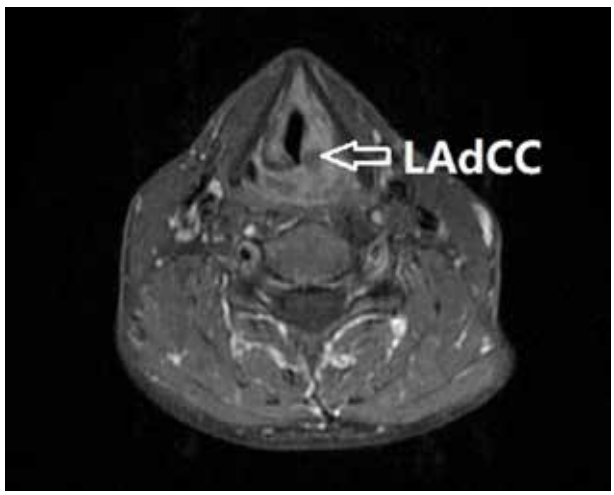

Fig. 7: MRI scan of case 2. The tumor anteriorly involves anterior commissure and paraglottic space, laterally infiltrating the right laryngeal ventricle and the right pyriform sinus, posteriorly affecting the right arytenoid cartilage and posterior commissure.

Postoperative clinical classification of case 1 was stage Ⅳ, $T_4N_0M_0$[13]; dissection margins and cervical lymph nodes were tumor-free. The patient refused post-operative radiotherapy; during the follow up the patient has remained free of tumor for two years.

Case 2

In October of 2014, a 47-year-old male presented to our department with a 2-year history of progressive pharyngolaryngeal paresthesias, pain and hoarseness, and 2-month history of symptom aggravation accompanied by inspiratory dyspnea.

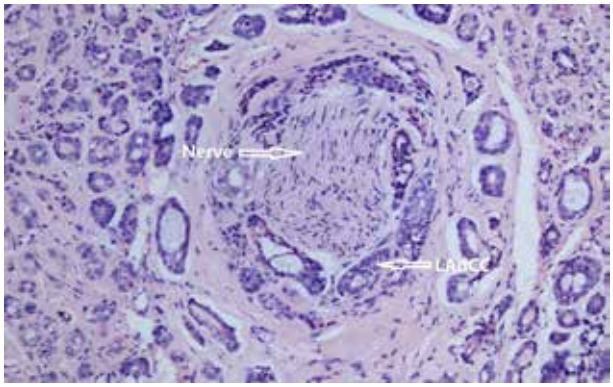

Fig. 8: Tumor invasion of perineural space in case 2. The pathological diagnosis is AdCC, sub-phenotype is cribriform. Tumor tissue is consisted of pseudocytos which is filled with mucin. Tumor submucosal infiltration and perineural invasion are observed.

Laryngoscopy revealed a huge mass on the right aryepiglottic fold with intact and uneven mucosal surface, the right vocal cord was fixed at para-median position, shown in Figure 6. MRI disclosed a solid, heterogeneous lesion with evidence of increased medium perfusion predominantly in the right aryepiglottic fold and the right vocal cord, shown in Figure 7.

Case 2 underwent a similar RFC-assisted total laryngectomy with bilateral functional neck dissection. Pathological diagnosis was a cribriform sub-phenotype of AdCC, stage ◎, $T_3N_0M_0$[13] with perineural invasion, shown in Figure 8. Dissection margins and neck lymph nodes were free of tumor. The patient declined adjuvant radiation therapy and there was no tumor relapse during follow-up.

DISCUSSION

During the early stage, LAdCC is usually asymptomatic probably due to tumor submucosal origin[2,7], and diagnosis is often made at stage ◎ or ◎[2]. Although there is usually no ulceration on tumor surface, it is very likely that cancer cells have already deeply invaded surrounding tissues and spread through the perineural space[1,8]. Complete investigation of tumor status is important.

CT and MRI are commonly used to evaluate primary tumor and potential metastasis because distant disseminations may occur quite often in the setting of negative neck lymph nodes, and lung is the most common organ to be involved[7].

Pathology and differential diagnosis

LAdCC may appear as a heterogeneous submucosal mass on CT/MRI scan, however histopathological examination can provide final diagnosis. There are three histological sub-phenotypes of LAdCC: cribriform, tubular and solid. The cribriform is the most common one, and the three sub-phenotypes may co-exist in one tumor. The tubular, cribriform and solid might signify the best, moderate and worst prognosis respectively[7].

Squamous cell carcinoma (SCC) is a very common laryngeal malignancy and basaloid SCC is one variant of SCC. The histologic presentation of basaloid SCC can be very similar to that of solid sub-phenotype of LAdCC, the morphologic overlapping between them may lead to misdiagnosis[8].

Immunohistochemical study may be helpful for differentiation between LAdCC and basaloid SCC. p63 or p40 are extensively expressed in basaloid SCC, but these two markers are negative in solid sub-phenotype of LAdCC[14].

Real time PCR can provide additional help in the diagnosis of LAdCC. In at least 80-90% of head-neck AdCC, there is a stable genetic translocation of t(6;9)(q22-23; p23-24) in the transcription-factors of MYB and NFIB. In the mutant transcription-factor of MYB-NFIB, the exon 14 of MYB is fused to the last coding exons of NFIB. The presence of MYB-NFIB fusion transcription-factors is a specific marker for the diagnosis of LAdCC[15-17].

A pathological diagnosis of LAdCC with high-grade transformation (LAdCC-HGT) is a specific aggressive tumor with rapid clinical course and poor prognosis due to high propensity of metastasis to local lymph nodes (more than 50%) and distant organs, and high incidence of tumor recurrence, and hence LAdCC-HGT needs individualized treatment[18].

Current trends in treatment

Adequate surgical resection as early as possible has been proved to have a beneficial impact on the prognosis of LAdCC[1]. 90% of the patients with LAdCC have surgical operation, and in 43% of all the surgically-treated patients, operation is the only treatment[7], and 57% of the patients treated solely by operation remain tumor free during follow-up[1].

Due to high propensity of tumor invasion along perineural bundles and spread submucosally, total laryngectomy has been routinely recommended. Partial laryngectomy is acceptable only for selected suitable patients, and salvaging total laryngectomy is reserved for recurrent cases. Subglottic LAdCC usually necessitates a total laryngectomy. Small glottic LAdCC confined within one vocal cord might be treated by partial laryngectomy[8].

If the cervical lymph nodes are palpable, functional neck dissection is usually performed[3,8]. Although palpable cervical lymph nodes are commonly presented, the incidence of cervical metastasis

proved by pathology is low, and prophylactic cervical lymphadenectomy is not routinely recommended. Radical neck dissection is reserved only for the patients with pathologically confirmed neck metastasis[8].

AdCC was reported to be radio-resistant in some patients[19]; in other patients, radiotherapy has been proved to prolong survival time and decrease recurrent rate indicating that AdCC is at least to some extent radiosensitive, but not radio-curable[2].

In the patients of Stage I with pathological evidence of negative dissection margins and no perineural invasion, postoperative-radiotherapy does not show to prolong survival time and reduce the incidence of tumor recurrence[1]. However, LAdCC is usually diagnosed at later stages, and postoperative-radiotherapy is usually recommended[3].

Limited data is available about radiotherapy alone as a primary treatment modality. In cases of un-resectable tumors or patients who do not accept surgery, photon-based radiation is a treatment option, but it is not as effective as the combination of surgery plus postoperative-radiotherapy. Chemotherapy is usually used as a palliative care for distant recurrent patients[20].

A combination of chemotherapy with proton-based radiation as primary treatment modality is another alternative option for regional tumor control and laryngeal function preservation, but the long-term prognosis still needs to be confirmed[20,21].

At present, surgery followed by postoperative-radiotherapy is still the standard treatment for LAdCC, which can confer patients the best prognostic outcomes[7]. However, the incidence of occult hematogenous dissemination to distant organs is up to 70%, and tumor recurrence may occur 10 years after surgical treatment. Five-year survival rate for stage I and II is 100%, whereas the rate for stage III and IV is 33%[22]. Tumor remaining after conventional surgery may be a main reason of poor prognosis, there is an urgent need to establish an effective treatment modality for the patients with advanced LAdCC.

RFC is a type of plasma-mediated tumor ablation. Since the working temperature is usually between 40 °C and 70 °C, the risk of an airway fire is very low. RFC uses high frequency energy and normal saline to generate a plasma field resulting in molecular disintegration and cell dissolving. RFC has been adopted in some E.N.T surgery[23], however there is no research to investigate RFC-assisted laryngectomy for the treatment of LAdCC.

The principal goal of our study is complete tumor-resection and long-term tumor-free survival time. Tumor remaining after surgery is probably due to the submucosal infiltration and perineural invasion of LAdCC[22]. The effective working thickness of RFC plasma field is up to 200 μm thick around active electrode[12,24], which indicates an extra 200 μm deep tissue dissolving and removal as compared to conventional surgical resection. After removal of LAdCC by conventional surgery, we used RFC to vaporize potentially remaining cancer tissue, hopefully to achieve an additional 200 μm of resection boundaries, to prevent possible residual cancer cells and further ensure pathological negative safety margins.

Small blood vessels are coagulated automatically, while larger vessels are sutured if necessary. There is almost no bleeding during the operation so that neurovascular structures are easily identified, which is particularly important for the resection of LAdCC, because the tumor tends to spread in perineural space. If nerve is involved by tumor, it can be dissected out with no tumor remaining.

On the other hand, RFC may play an important role in anti-tumor immunity to kill potential residual cancer cells after surgery. Molecular disintegration induced by RFC may promote aggregation of macrophages, improve phagocytosis, and strengthen the activity of MHC class II for T cell interaction to generate tumor-specific immune responses. This boosting of anti-tumor immunity induced by RFC may provide additional therapeutic effect to destroy possible remaining cancer cells after surgery[10].

Other advantages of RFC presented in our study includes fast and complete tumor removal, less intra-operative complication, minimal generation of inflammation and no formation of granulation tissue, and rapid post-operative recovery[25]. Coblation has been shown to enhance wound healing[26], no pharyngeal fistula occurs in our patients. In our experience, LAdCC can be removed accurately and completely with appropriate maneuver of RFC, RFC-assisted laryngectomy is a promising treatment modality for LAdCC.

CONCLUSION

We had two advanced cases in our study, one case was stage III, $T_3N_0M_0$, another case was stage stage IV, $T_4N_0M_0$, both of them were treated by radiofrequency coblation assisted laryngectomy and they have been tumor-free for over 5 years. Radiofrequency coblation assisted surgery might be a promising technology for the treatment of malignant tumor.

ACKNOWLEDGMENT

Statement of Ethics

Our study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

All the patients have given their written informed consent to publish their case (including publication of images). Our study protocol was approved by the institute ethic committee about human research.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Funding: This research is supported by Natural Science Foundation of Fujian Province 2019J01622.

All authors contributed equally.

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Case Report

A different perspective on the treatment of branchial cleft cysts, which are very rarely located in the nasopharynx: a case series

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Kuwait Medical Journal 2024; 56 (4): 340 - 344

ABSTRACT

Nasopharyngeal branchial cleft cysts are very rare. There is no consensus about the approach to these pathologies. The problem that makes surgery difficult is its possible proximity to vital vascular structures such as internal carotid in the deep plane and located laterally. We aimed to present our series of three patients who were diagnosed with nasopharyngeal branchial cyst and operated by transnasal endoscopic method by determining the safe surgical margin with the help of Doppler ultrasonography. Three male patients, who had various complaints such as difficulty breathing through the nose and sleep problems, were operated on with a transnasal endoscopic approach supported by 20MHz Doppler ultrasonography due to cystic formation in the nasopharynx. Histopathological evaluations were reported as a nasopharyngeal branchial cleft cyst. Doppler ultrasonography assisted transnasal endoscopic approach can be applied in the treatment. This approach both shortens the duration of surgery and minimizes the risk of neurovascular injury.

KEY WORDS: doppler ultrasonography, nasopharyngeal branchial cleft cyst, transnasal endoscopic approach

INTRODUCTION

Nasopharyngeal branchial cleft cysts usually originate in the second branchial cleft and are very rare[1,2]. They are usually asymptomatic or manifest themselves with nasal congestion by taking up space in the nasopharynx. There is no consensus about the approach to these very rare pathologies in the literature[3]. The problem that makes surgery difficult is its possible proximity to vital major vascular structures such as internal carotid artery in the deep plane and located laterally[4]. This study aims to present our series of three cases of nasopharyngeal branchial cyst diagnosed with nasopharyngeal branchial cyst and excised transnasally and endoscopically by determining a safe margin with the help of Doppler ultrasonography. Written informed consent was obtained from the patients.

CASE REPORT

Case 1

A 32-year-old male patient was admitted with complaints of long-standing nasal congestion, sleeping with his mouth open, snoring and lack of hearing from the right ear. Ear examination was normal. Endoscopic nasopharynx examination revealed a smooth-surface lesion covering the right choana in the nasopharynx. Maxillofacial magnetic resonance imaging (MRI) of the patient (Figures 1, 2 and 3) revealed a hyperintense 16x26 mm cystic lesion on the right lateral side of the nasopharynx. Paranasal computed tomography (CT) showed a 28x24 mm hypodense formation filling the right fossa of Rosenmüller. The patient was operated on. A choana-level mass was reached transnasally by endoscopy in the operation. First, a puncture was performed with a 20-gauge needle. The anterior

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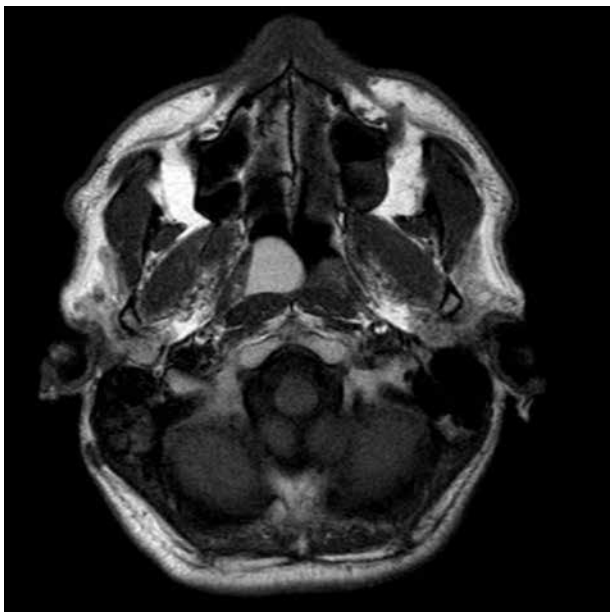

Figure 1: Axial magnetic resonance imaging sections of case 1.

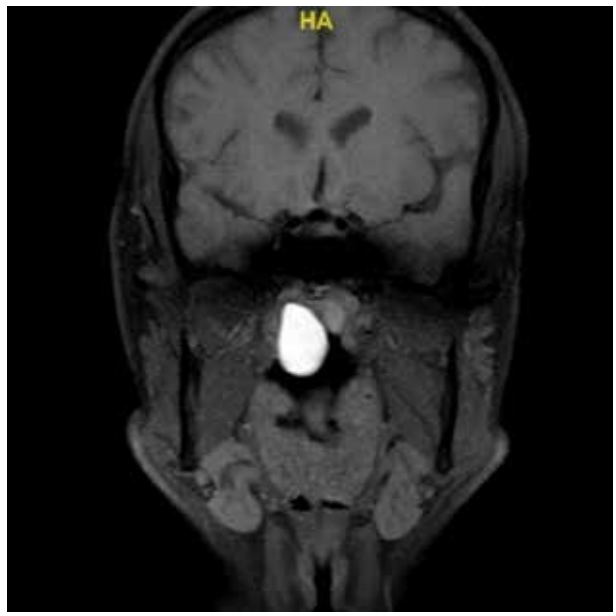

Figure 2: Coronal magnetic resonance imaging sections of case 1.

wall of the cyst was opened with a microdebrider upon cystic content in the puncture. The content was aspirated. The cyst wall was carefully dissected from the fossa of Rosenmüller and basilar fascia. Excision was completed with microdebrider by controlling the border with Doppler ultrasonography (VTI Doppler Transceiver 20 MHz, Vascular Technology Inc., Nashua, USA) due to the possibility of proximity to vascular structures while working at the posterolateral border. Histopathological examination shows chronic inflammation and fibrosis accompanied by lymphoid aggregates on the wall of the cyst lined by squamous epithelium and respiratory epithelium. The case was reported to be compatible with the branchial cleft cyst with the current histomorphological results. No recurrence was observed during the approximately 2-year follow-up of the patient.

Case 2

A 39-year-old male patient was admitted with complaints of right nasal congestion and snoring. Endoscopic nasopharynx examination of the patient

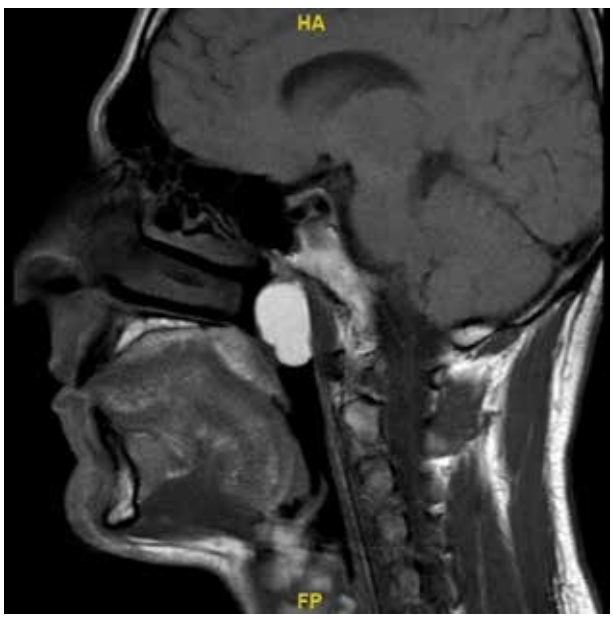

Figure 3: Sagittal magnetic resonance imaging sections of case 1.

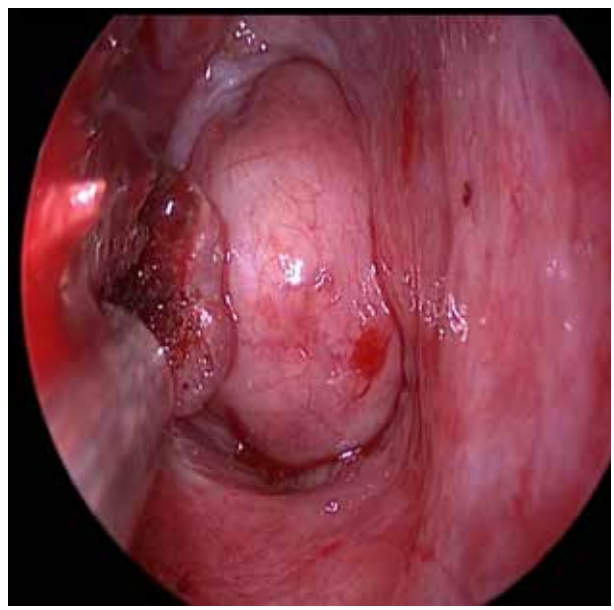

Figure 4: Endoscopic image of smooth-surface formation originating from nasopharynx obliterating the right choana.

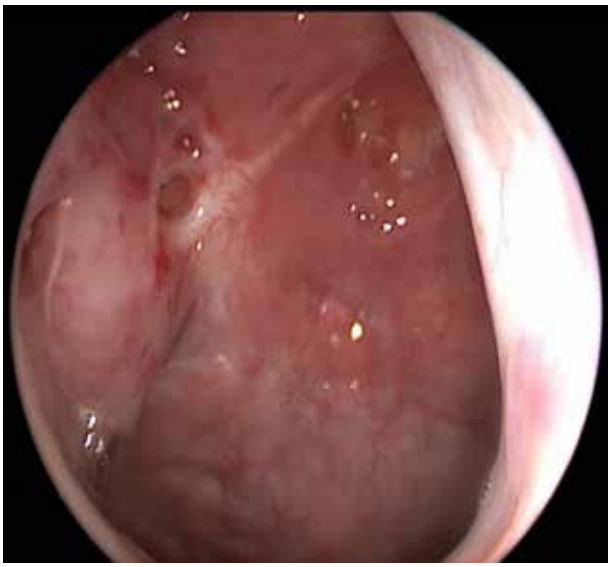

Figure 5: Endoscopic examination of the patient after 11 months postoperatively.

revealed a smooth-surface lesion crossing the midline filling the right choana (Figure 4). MRI revealed a hyperintense 21x17 mm non-contrast uptake cystic lesion in the T2A series filling the right choana on the right side of the nasopharynx. Excision was applied to the patient who decided to undergo the operation with an approach similar to the one in the first case. Histopathological examination revealed findings similar to Case 1 and Case 3. The case was reported to be compatible with the branchial cleft cyst with the current histomorphological results. No recurrence was observed during the approximately 11-month follow-up of the patient (Figure 5).

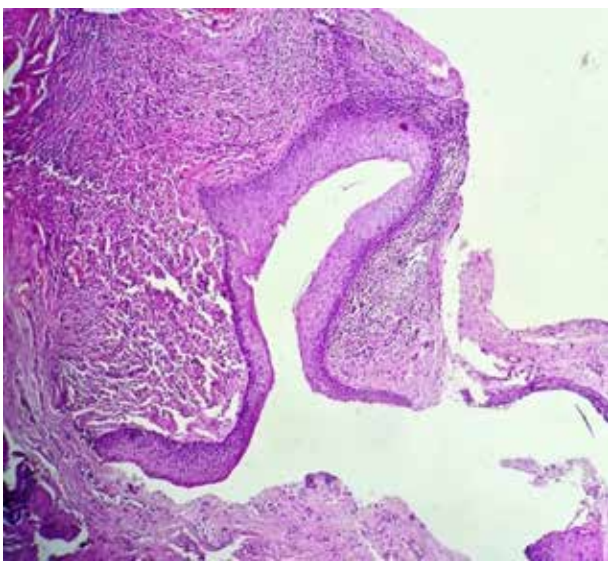

Figure 6: Chronic inflammation and fibrosis on the cyst wall lined by squamous epithelium (H&E x100).

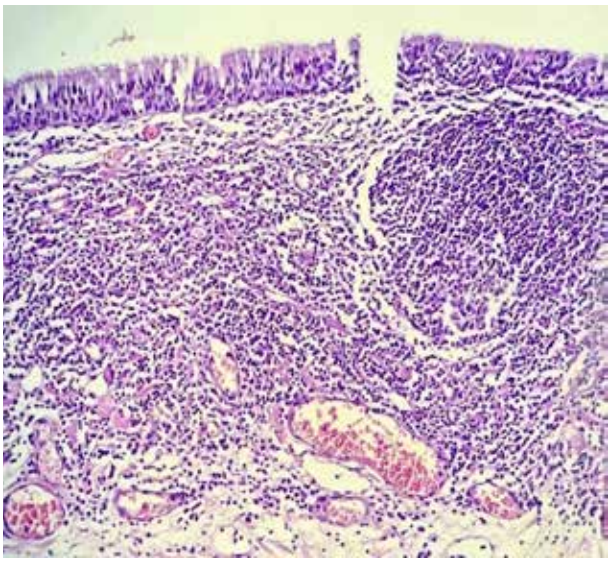

Figure 7: Diffuse lymphoid infiltrate with lymphoid follicle on the cyst wall lined by respiratory epithelium (H&E x200).

Case 3

A 37-year-old male patient was admitted with complaints of long-standing nasal congestion, sleeping with his mouth open and snoring. Nasopharynx examination of the patient without any additional complaints revealed a smooth-surface lesion crossing the midline filling the right nasal passage. MRI revealed a hyperintense 31x22 mm cystic lesion on the right lateral and posterior nasopharynx. Paranasal CT revealed 32x22 mm cystic formation narrowing the passage in the nasopharynx. Excision was performed similar to patients 1 and 2. The cyst-lining epithelium is commonly characterized by respiratory epithelium and squamous epithelium in focal areas in histopathological examination. Histopathological examination revealed findings similar to Case 1 and Case 2 (Figures 6, 7). The case was reported to be compatible with the branchial cleft cyst with the current histomorphological results. No recurrence was observed during the approximately 1.5-year follow-up of the patient.

DISCUSSION

Second branchial cleft anomalies can be seen in any area along the embryological pathway to the sternocleidomastoid muscle and tonsillar fossa in the anterior region of the neck. They can also be seen less frequently in the parapharyngeal and nasopharynx. Proctor classified the 2nd branchial cysts into 4 categories. Accordingly, type 1 sternocleidomastoid muscle is below the cervical fascia at its anterior border; type 2 is the most common and is in contact with large vessels below the investing layer of the deep cervical tree; type 3 extends from the internal and

external carotid to the pharyngeal wall and lastly, type 4 is adjacent to the pharyngeal wall and medial to the large vessels[5]. Accordingly, nasopharyngeal branchial cysts fit type 4 of the second branchial cleft cysts[2].

Branchial cleft cysts located in the nasopharynx are usually asymptomatic and can usually grow and become symptomatic after the second decade. Patients apply to the outpatient clinic with nasal congestion[6]. All three of our patients presented to the outpatient clinic with nasal congestion and sleep disturbance.

Retention cysts, sphenoid sinus mucocele, Tornwaldt cyst, Rathke's cleft cyst, chordoma, malignancy and nasopharyngeal bronchogenic cysts should be considered in the differential diagnosis of nasopharyngeal cysts. Tornwaldt cysts are usually located in the midline while nasopharyngeal branchial cleft cysts are located close to the Eustachian tube opening and laterally[1]. The nasopharyngeal branchial cyst was right-sided in all three cases we operated on.

Smooth-surface mass is observed in the examination. The radiological evaluation shows a low-density cystic mass image on CT[7]. MRI shows hyperintense appearance in T2-weighted sections whereas lower signal intensity is observed in T1-weighted sections. MRI is useful in showing the content of the cyst, soft tissues and vascular adjacents.

Histopathologically, the majority of the branchial cleft cysts are lined by squamous epithelium, and the presence of nodular or diffuse lymphoid infiltrates, which often include a germinal center, is typical on the cyst wall. Some cysts may be lined by respiratory epithelium, less frequently with transient or both squamous and respiratory epithelium. It is stated that nasopharyngeal retention cysts do not have a wall covered with epithelium whereas lymphoid tissue is not observed in the Tornwaldt cyst[7,9]. There are two types of epithelium in all three cases we presented.

Total surgical excision is expressed as the ideal treatment method recommended. Total surgical excision can be performed through transcervical, transoral, transpalatal and transmandibular routes. While transcervical, transpalatal and transmandibular approaches allow more comprehensive monitoring of the surgical site according to the size of the cyst, it has the potential for complications such as scarring and velopharyngeal insufficiency. There is a risk of neurovascular injury in total excision due to the adjacency of the area where the branchial cleft cysts are located even though total excision is less invasive with the transoral approach compared to previous approaches. Marsupialization by transoral or transnasal route has recently been preferred. Powered instruments can also be used during excision as previously described. The likelihood of complications is lower and the surgery can be completed in a shorter time with these approaches[3,1,7]. Excision was performed with a microdebrider in three of our cases. Near-total cyst excision was performed transnasally with endoscopy in all three cases. Doppler ultrasonography was used during surgery to avoid vascular complications. 20 MHz microvascular Doppler systems are used to find vascular structures in various surgical areas by receiving instantaneous vascular flow sound. It is frequently used in neurosurgery and urology. All three patients were kept in the hospital for precautionary purposes for one day after the surgery, no complications such as bleeding were observed. We believe that further studies are needed on the use of this device in the field of otorhino-laryngology.

CONCLUSION

There is no consensus about the approach to these very rare pathologies in the literature. The problem that makes surgery difficult is its possible proximity to vital major vascular structures such as internal carotid artery in the deep plane and located laterally. This study is the publication reporting that this device was used for the first time in the head and neck area. We believe that it will guide its use in recognizing vascular structures in many surgeries in the field of otorhino-laryngology for this reason. That is why we used this device during surgery. However, near-total excision or marsupialization is recommended to avoid major complications if there is a cyst too close to the large vessels.

ACKNOWLEDGMENT

Author contribution: Bilal Sizer and Argün Ediz Yorgancılar: author and surgeon; Pınar Ergen: author and histopathology findings with microscope.

Conflicts of interest: The authors have no competing interests.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not for profit sectors.

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Case Report

Recurrent parotid abscess in transfusion dependent thalassemia major: A case report

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Kuwait Medical Journal 2024; 56 (4): 345 - 347

ABSTRACT

Recurrent parotid abscess is a rare presentation with limited cases published pertaining to it. We report a case of a 31-year-old female with transfusion dependent thalassemia major who presented with recurrent episodes of parotid abscess. She responded well to antibiotics only treatment without surgical drainage. Given the relatively low occurrence of recurrent parotid abscess, a contributing factor such as immunocompromised state seen in thalassemia should be considered.

KEY WORDS: recurrent parotid abscess, transfusion dependent thalassemia major

INTRODUCTION

Parotid abscess is an uncommon pathology whereby suppurative changes usually due to bacterial infection occur at intraparotid, periparotid lymph nodes or parotid glandular parenchyma[1].

Recurrent parotid abscess is rare and has been related to systemic diseases, eg: thalassemia[2]. Thalassemic patients show higher risk towards recurrent infections due to immunosuppression caused by iron overload[3-5]. Clinically, patients often present with warm and erythematous parotid swelling associated with pain and fever[6]. Initial management of parotid abscess involves hydration, nutritional support, analgesics, sialagogues, good oral hygiene and antibiotic therapy. Surgical drainage is indicated upon failure of medical treatment or abscess with extensive involvement (involving facial nerve or adjacent structures)[6].

CASE REPORT

A 31-year-old female presented with right parotid mass which was rapidly enlarging and painful for 2 months. She has a history of recurrent self-limiting right parotid swelling for more than 10 years. Further history noted that she was diagnosed with beta-thalassemia major at the age of 2. She has been transfusion dependent since then and had splenectomy at the age of 15. Currently, she is on iron-chelating treatment (deferoxamine) and activin receptor ligand trap (luspatercept) for iron overload.

Clinical examination showed a painful mass in the right parotid region measuring 3cm x 2cm. The overlying skin was erythematous and warm to touch. There was no facial nerve involvement and dental hygiene was good. No discharge was seen upon milking along Stenson's duct. Subsequent ultrasound showed right parotid multiloculated collection largest measuring 0.5 cm with inflammatory nodes. Her condition resolved clinically with 1 week of intravenous empirical antibiotic (amoxicilin clavulanate).

Unfortunately, she was re-admitted 1-month later with similar presentation. Ultrasound showed right parotid multiloculated collections largest measuring 1.3 cm. She was again given the same empirical antibiotic (amoxicilin clavulanate) and clinically improved without surgical drainage after 5 days.

After another 1 month, she presented with another episode of right parotid swelling. Following that, a

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CT scan was done revealing a thick rim enhancing collection within the superficial lobe of right parotid gland largest measuring 2.8 cm. In order to establish the causative pathogen, we attempted to aspirate the collection via ultrasound guidance. However, no sample was obtained as the collection was too small. Intravenous ampicillin/sulbactam was initiated and subsequently, the parotid abscess resolved both clinically and with confirmation of ultrasound. Eventually, she was discharged well without recurrence after 6 months of follow up.

DISCUSSION

This case highlights a transfusion-dependent thalassemia major patient who has been suffering recurrent episodes of unilateral parotid abscess but responsive to antibiotic without surgical drainage. To date, there are limited case reports published on recurrent parotid abscess. In a study conducted by Horowitz *et al*, most recurrent suppurative parotiditis cases identified are associated with immunosuppressive conditions (Eg: recurrent skin infections, insulin-dependent diabetes mellitus, tetralogy of Fallot)[2]. This is the first reported case of recurrent parotid abscess in a patient with thalassemia.

Transfusion dependent thalassemia has been associated with higher risk of infection due to high ferritin levels (>1000 ng/ml), deranged liver functions, history of splenectomy (more than 10 years) and early onset for iron chelating therapy[3-5]. It is believed that iron overload in transfusion-dependent thalassemia may result in impairment of macrophage and neutrophil function[7]. It may also cause immune suppression via inhibition of interferon-gamma activity, reduced phagocytosis, decreased CD 4 T-cell numbers, suppression of immunoglobulin secretion and complement system function, therefore increasing the risk of infection[8].

Klebsiella infection is the most common cause of infection among thalassemia patients[3-5]. In our local data, *Staphylococcus aureus* and *Klebsiella species* are the common organisms isolated from parotid abscess[9]. Thalassemia patients are more susceptible to salivary gland infection as iron overload increases the virulence of organisms such as the *Klebsiella species*[5]. Besides that, iron overload causes iron deposition in parotid secretory cells. Goldfarb *et al* has revealed histopathological evidence of iron deposits in the serous cells of parotid glands, which may result in cellular damage in transfusion dependent patients[10]. These suggest the predisposition towards parotid gland infection among thalassemia patients.

Traditionally, surgical intervention is indicated upon the manifestation of parotid abscess, specifically in cases that lack improvement after antibiotic therapy, involvement of facial nerve or adjacent fascial plane, septicemia and frank abscess, formation[6,11]. Rapid surgical drainage is advocated in certain cases to minimize complications and improve recovery time[12]. However, a study done in Korea showed no parotid abscess recurrence among their patients who had antibiotic treatment only and conservative treatment were preferred for parotid abscesses of smaller size (less than 3 cm)[12]. Our patient had recurrent parotid abscess which responded well to intravenous antibiotics upon every admission. Surgical drainage in her situation may not be justified as complications that can potentially result in prolonged recovery secondary to poor wound healing may be foreseen[9].

CONCLUSION

Recurrent parotid abscess is an uncommon presentation and may manifest in immunocompromised individuals such as those with thalassemia major. Surgical drainage is commonly done for parotid abscess. However, in certain cases, conservative management with antibiotics can produce a similarly good outcome.

ACKNOWLEDGMENT

The authors would like to thank the Director General of Health Malaysia for his permission to publish this case report.

Author contributions: Alex Ho Zxi Jian: case study design, data acquisition, drafting of manuscript, final approval of the version to be published and agreement to be accountable for all aspects of the work. Teh Hui Mon: Case study design, revision of the manuscript for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work.

Funding: None

Conflict of interest: The authors declare no conflict of interest.

Informed consent: Informed consent of the patient was obtained. Formal consent is not required.

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Letter to Editor

Can the development of lung COVID be prevented after COVID-19 infection?

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Kuwait Medical Journal 2024; 56 (4): 348

Dear Editor,

The World Health Organization defines long COVID as starting three months after the initial COVID-19 infection. The causes of long COVID are not yet fully understood. Hypotheses include lasting damage to organs and blood vessels, problems with blood clotting, neurological dysfunction, persistent virus or a reactivation of latent viruses and autoimmunity[1]. Generally, initial symptoms of long COVID symptoms include fatigue (29%), muscle pain, palpitations, cognitive impairment (28%), dyspnea (21%), anxiety (27%), chest pain and arthralgia (18%). Although several guidelines on long COVID management have been released, there remains a large practical gap and specific treatments are not reviewed. Histamine antagonists have been used to relieve long COVID associated symptoms[2].

Dietary supplements may also have beneficial effect in modulating systemic inflammation and immunity. Natural flavonoids such as luteolin and quercetin are promising immunomodulatory agents which have showed inhibitory effects on mast cells[3]. Thymoquinone (TQ) is a bioactive component obtained from Nigella sativa. TQ has demonstrated antibacterial, anti-inflammatory, anti-oxidant, neuroprotective and antiapoptotic effects. In addition, it has been shown that opioid-active peptides such as hemorphins are activated by TQ and thus have an inhibitory effect on ACE receptors[4]. Therefore, TQ can block SARS-CoV-2 entry by blocking the ACE2 receptor.

Treatment of patient groups with a high risk of developing lung COVID (advanced age, history of intensive care hospitalization, long-term oxygen need, etc.) after COVID-19 infection with TQ may be protective against lung COVID. For these reasons, further clinical studies are required.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2024; 56 (4): 349 - 351

Chronic kidney disease in Kuwait: a multicenter study of two cohorts with different levels of access to public healthcare

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BMC Nephrol. 2024 Oct 16;25(1):356. doi: 10.1186/s12882-024-03794-6.

INTRODUCTION
Kuwait has a large expatriate community who experience both restricted access to public health services and lower income than Kuwaiti citizens. Given these conditions, we examined differences in characteristics and management of chronic kidney disease (CKD) between Kuwaitis and expatriates.

METHODS
Clinical and laboratory data for adult CKD Stages 3-5 not on dialysis (CKD 3-5 ND) patients with native kidneys attending nephrology clinics in all Ministry of Health hospitals collected from January 1, 2022, to December 31, 2022. Cohort was then divided into Kuwaiti patients and expatriates patients for comparison.

RESULTS
We collected data from 2,610 patients (eGFR: 30.8 ml/min/1.73m2; age: 62.6 years; males: 56.7%; Kuwaitis: 62.1%). Kuwaitis were older (63.94 vs. 60.3 years, $p < 0.001$), with lower mean eGFR (30.4 vs. 31.5 ml/min/1.73m2, $p = 0.052$) than non-Kuwaitis, however, Kuwaitis had lower mean blood pressure (137.2/76.5 vs. 139.1/78.9 mmHg, $p = 0.006$), lower HbA1c in diabetics (7.59 vs. 7.82%, $p = 0.010$), and better lipid profile despite higher body mass indexes (29.6 vs. 28.9 kg/m2, $p = 0.002$). Both groups had high diabetes mellitus and hypertension rates. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were used in only 22.6% and renin-angiotensin-aldosterone system inhibitors (RAASi) in only 46.2%.

CONCLUSION
CKD 3-5 ND is caused by diabetes mellitus in 56.6% of cases, and the majority have hypertension. In our study, non-Kuwaitis had higher eGFR; however, restricted public healthcare access and lower income can lead to an unhealthy diet and suboptimal care, which may cause higher blood pressure, higher HbA1c, and a higher dyslipidemia rate. RAASi and SGLT2i utilization must increase to combat CKD, and antihypertensive selection must improve.

Health Care Access, Socioeconomic Status, and Acute Kidney Injury Outcomes: A Prospective National Study

Ali AlSahow [1], Omar Alkandari [2], Anas AlYousef [3], Bassam AlHelal [4], Heba AlRajab [5], Ahmed AlQallaf [6], Yousif Bahbahani [7], Monther AlSharekh [8], Abdulrahman AlKandari [1], Gamal Nessim [7], Bassem Mashal [1], Ahmad Mazroue [3], Alaa Abdelmoteleb [6], Mohamed Saad [5], Ali Abdelzaher [8], Emad Abdallah [4], Mohamed Abdellatif [5], Ziad ElHusseini [4], Ahmed Abdelrady [6]

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Kidney Med. 2024 Jul 10;6(9):100867. doi: 10.1016/j.xkme.2024.100867. eCollection 2024 Sep.

RATIONALE & OBJECTIVES
Acute kidney injury (AKI) incidence and outcome in Kuwait are unknown. Moreover, non-Kuwaitis, who represent 66% of the population, have lower income, and their access to public health services is restricted compared with Kuwaitis who have free full access.

STUDY DESIGN
Observational prospective multicenter cohort study.

SETTING & PARTICIPANTS
Adult inpatients with AKI in 7 public hospitals from January 1 to December 31, 2021.

EXPOSURE
AKI identified using Kidney Disease: Improving Global Outcomes serum creatinine-based criteria.

OUTCOMES
For hospitalized patients with AKI, the outcomes included 30-day outcomes of mortality, need for dialysis, kidney recovery rates, and differences in outcomes between Kuwaitis and non-Kuwaitis.

ANALYTICAL APPROACH
A backward stepwise multiple logistic regression analysis was performed to assess possible independent risk factors for the outcomes.

RESULTS
We recruited 3,744 patients (mean age: 63 years; mean baseline estimated glomerular filtration rate [eGFR]: 66.7 mL/min; non-Kuwaitis: 42.3%), representing 3.2% of hospitalizations and 19.5% of intensive care unit (ICU) admissions. Non-Kuwaitis were significantly younger (57.6 vs 66.9 years), with higher baseline eGFR (73.1 vs. 62 mL/min), more frequent community acquired AKI (53.8% vs 46.7%), and AKI in summer (34.7% vs 26.9%). Dialysis was provided to 33.5% of patients, with a higher need for non-Kuwaitis (35.5% vs 32.1%). At 30 days, 34.4% of patients died, representing 24.8% of hospital mortality and 59.8% of ICU mortality. No differences in mortality or kidney recovery were noted between Kuwaitis and non-Kuwaitis. Low eGFR did not affect the mortality rate.

LIMITATIONS
Observational nature and short follow-up period of 30 days only.

CONCLUSIONS
AKI was associated with high dialysis need and mortality. Non-Kuwaitis accounted for less cases despite representing 66% of the population because they were younger with higher baseline eGFR and fewer comorbid conditions. Non-Kuwaitis had higher rates of community acquired AKI and AKI in summer and a higher need for dialysis but had similar mortality and complete kidney recovery rates.

Varicella Pneumonia in Immunocompetent Adults: Symptomatic and Asymptomatic Cases

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Case Reports Cureus. 2024 Sep 7;16(9):e68891. doi: 10.7759/cureus.68891. eCollection 2024 Sep.

Varicella zoster virus (VZV) is an enveloped, linear double-stranded DNA virus. It belongs to the Herpesviridae family and can manifest as primary varicella infection or secondary infection, also known as herpes zoster. Varicella pneumonia is an uncommon but potentially life-threatening complication of primary varicella infection. It mainly affects adults, and, if left untreated, the mortality rate is high. We report two cases involving adult male patients who presented with a generalized widespread vesicular rash compatible with primary varicella. Each patient had a different clinical presentation; the first patient had respiratory symptoms, while the second patient did not. Chest radiographs of both patients showed bilateral infiltrates. Treatment was initiated with the administration of intravenous acyclovir with a very good response. This report of two cases highlights the importance of early detection and prompt treatment of varicella-related complications, especially in higher-risk patients, to reduce morbidity and mortality and improve overall clinical outcomes. We also aim to reinforce the importance of immunization, which would aid in reducing the incidence of vaccine-preventable diseases such as varicella and its life-threatening complications.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2024; 56 (4): 352 - 362

International Conference on **Medical and Health Sciences**
Dec 01, 2024
United Kingdom, Edinburgh
Organized by: SciencePlus
Email: papers.scienceplus@gmail.com

International Conference on **Medical Health Science, Pharmacology & Biotechnology**
Dec 01, 2024
United States, New York
Organized by: ISSRD
Email: papers.issrd@gmail.com

International Conference on Recent Advancement in **Medical Education, Nursing, and Health Sciences**
Dec 03, 2024
South Korea, Seoul
Organized by: IRF conference
Email: info.irfconference@gmail.com

International Conference on **Cardiology and Cardiovascular Medicine**
Dec 03, 2024
Australia, Ballarat
Organized by: The International Society for Researchers and Doctors
Email: info.theisrd@gmail.com

International Conference on **Veterinary Forensic Medicine**
Dec 03, 2024
United States, Las Vegas, Nevada
Organized by: Science Guru
Email: info.scienceguru@gmail.com

International World Research Congress on **Dentistry and Oral Health**
Dec 05, 2024
Singapore, Singapore
Organized by: Biofora
Email: info@biofora.org

International Conferences on Advances in **Nursing Science, Medical and Health Care**
Dec 05, 2024
Thailand, Bangkok
Organized by: Theires
Email: info@theires.org

International Conference on **Medical Health Science, Pharmacology & Biotechnology**
Dec 06, 2024
Singapore, Singapore
Organized by: ISSRD
Email: papers.issrd@gmail.com

International Conference on **Bioinformatics, Biomedicine, Biotechnology and Computational Biology**
Dec 06, 2024
Scotland, Glasgow
Organized by: Eurasia Web
Email: info@eurasiaweb.com

International Congress on **Physical Activity and Public Health**
Dec 06, 2024
United Kingdom, Labrador
Organized by: Research Era
Email: info.researcheraconference@gmail.com

International Conferences on Advances in **Nursing Science, Medical and Health Care**
Dec 07, 2024
New Zealand, Wellington
Organized by: Theires
Email: info@theires.org

International Conference on **Animal Health and Veterinary Medicine**
Dec 07, 2024
Saudi Arabia, Jeddah
Organized by: Global Science Networks
Email: info.globalsciencenetworks@gmail.com

International Conference on **Animal Health** Surveillance
Dec 07, 2024
Russia, Saint Petersburg
Organized by: Science and Research
Email: summit.scienceandresearch@gmail.com

International Conference on **Bioinformatics, Biomedicine, Biotechnology and Computational Biology**
Dec 08, 2024
United States, Detroit, Michigan
Organized by: Eurasia Web
Email: info@eurasiaweb.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
Dec 09, 2024
Qatar, Doha
Organized by: GSRD
Email: info.gsrd@gmail.com

International Conference on **Stem Cells, Regenerative Medicine and Tissue Engineering**
Dec 09, 2024
France, Paris
Organized by: Sciconx
Email: stemcells@sciconxevents.com

International Conference on **Nutrition & Health**
Dec 11, 2024
United Arab Emirates, Abu Dhabi
Organized by: Conference Online
Email: info.conferenceonline@gmail.com

International Conference on **Medical, Healthcare, and Pharmaceutical Science**
Dec 11, 2024
United Arab Emirates, Abu Dhabi
Organized by: Conference Online
Email: info.conferenceonline@gmail.com

International Conference on **Healthcare Innovation and Medical Sciences**
Dec 12, 2024
United Arab Emirates, Dubai
Organized by: Biofora
Email: info@biofora.org

Global **Cardiology and Healthcare** Summit
Dec 12, 2024
United Arab Emirates, Dubai
Organized by: Biofora
Email: info@biofora.org

The 7th KNC & 14th GCC **Neurology** Conference
Dec 12-14, 2024
Kuwait, Grand Hyatt Hotel
Organized by: Kuwait Neurology Society
Website: www.kuwaitneurology.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Dec 15, 2024
Japan, Fukuoka
Organized by: WRFER
Email: contact.wrfer@gmail.com

International Conference on **Clinical Neuropharmacology, Neuroscience and Medicine**
Dec 15, 2024
United States, Texas
Organized by: All Conference Series
Email: info.allconferenceseries@gmail.com

2nd International Summit on **Nursing and Healthcare**
Dec 16, 2024
France, Paris
Organized by: ISNH2024
Email: isnh2024@spectrumconferences.com

International Conference on **Bioinformatics, Biomedicine, Biotechnology and Computational Biology**
Dec 17, 2024
Mali, Sikasso
Organized by: Eurasia Web
Email: info@eurasiaweb.com

International Conference on **Healthcare and Clinical Gerontology**
Dec 18, 2024
South Korea, Daegu
Organized by: Sciencefora
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International Conference on **Physical Therapy and Sports Medicine**
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International Conference on **Pediatrics and Healthcare**
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India, Delhi
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Email: info.scienceguru@gmail.com

International Conference on **Recent Advancement in Medical Education, Nursing, and Health Sciences**
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Turkey, Istanbul
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Email: info.irfconference@gmail.com

International Conference on **Recent Advancement in Medical Education, Nursing, and Health Sciences**
Dec 22, 2024
Australia, Sydney
Organized by: IRF conference
Email: info.irfconference@gmail.com

International Conference on **Psychology and Mental Health**
Dec 22, 2024
United States, Philadelphia, Pennsylvania
Organized by: Science and Research
Email: summit.scienceandresearch@gmail.com

International Conference on **Laboratory Medicine & Pathology**
Dec 22, 2024
Canada, Oshawa
Organized by: United Science Research Society
Email: info.usrsociety@gmail.com

International Conference on **Gynecology Obstetrics and Women's Health**
Dec 23, 2024
Denmark, Skagen
Organized by: Academic Research Network
Email: info.academicresearchnetwork@gmail.com

World Conference on **Orthopedics, Sports Medicine and Rehabilitation**
Dec 24, 2024
United States, Atlanta, Georgia
Organized by: Science and Research
Email: summit.scienceandresearch@gmail.com

International Conference on **Public Health and Epidemiology**
Dec 25, 2024
South Korea, Incheon
Organized by: All Conference Series
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International Conference on **Healthcare and Clinical Gerontology**
Dec 26, 2024
China, Macau
Organized by: Sciencefora
Email: info.sciencefora@gmail.com

International Conference on **Nanomedicine and Nanomaterials**
Dec 26, 2024
Sweden, Malmo Municipality
Organized by: Research Era
Email: info.researcheraconference@gmail.com

International Conference on **Recent Advances in Medical, Medicine and Health Sciences**
Dec 27, 2024
Canada, Toronto
Organized by: WRFER
Email: contact.wrfer@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Dec 28, 2024
Kuwait, Kuwait City
Organized by: Academics world
Email: info@academicsworld.org

International Conference on Recent Advances in **Medical and Health Sciences**
Dec 30, 2024
Canada, Vancouver
Organized by: Academics world
Email: info@academicsworld.org

International Congress on **Physical Activity and Public Health**
Dec 31, 2024
Indonesia, Bali
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Email: info.researcheraconference@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jan 01, 2025
Australia, Sydney
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International Conference on **Animal Biotechnology and Veterinary Medicine**
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Japan, Kitakyushu
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International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jan 04, 2025
Switzerland, Geneva
Organized by: WRFER
Email: contact.wrfer@gmail.com

International Conference on **Bioinformatics, Biomedicine, Biotechnology and Computational Biology**
Jan 04, 2025
France, Lyon
Organized by: Eurasia Web
Email: info@eurasiaweb.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jan 05, 2025
Japan, Tokyo
Organized by: WRFER
Email: contact.wrfer@gmail.com

International Conference on **Health Policy Statistics**
Jan 06, 2025
United States, California
Organized by: American Statistical Association
Email: asainfo@amstat.org

International Conference on **Physical Education, Health and Sports**
Jan 07, 2025
Belgium, Bruges
Organized by: All Conference Series
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International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Jan 08, 2025
India, Aizawl, Mizoram
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1st Adan **Internal Medicine** Conference 2025
Jan 10-11, 2025
Kuwait, Waldorf Astoria
Organized by: Adan Hospital
Website: www.aim-2025.com

International Conference on **Infectious Diseases and Nanomedicine**
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Italy, Milan
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International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Jan 17, 2025
India, Satara, Maharashtra
Organized by: ISSRD
Email: papers.issrd@gmail.com

1st Sabah Hospital **Scientific Day**
Jan 18, 2025
Kuwait, Grand Hyatt Hotel
Organized by: Sabah Hospital - Medical Department

International Conference on **Animal Biotechnology and Veterinary Medicine**
Jan 18, 2025
Australia, Perth
Organized by: Japanese Society for Academic Research and Publication
Email: info.jsarap@gmail.com

International Conference on **Veterinary Forensics, Veterinary Forensic Medicine and Pathology**
Jan 18, 2025
United States, Los Angeles, California
Organized by: United Research
Email: info.unitedresearch@gmail.com

International Conference on **Epidemiology & Public Health**
Jan 19, 2025
United States, Ann Arbor, Michigan
Organized by: Meeting fora
Email: info@meetingfora.com

International Conference on **Healthcare and Clinical Gerontology**
Jan 19, 2025
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Jan 21, 2025
Singapore, Singapore
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4th Kuwait Pediatric **Stem Cell & Cellular Therapy** Conference
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Kuwait, Four Seasons Hotel
Website: https://psctckw.com

International Conference on **Bioinformatics, Biomedicine, Biotechnology and Computational Biology**
Jan 22, 2025
Italy, Naples
Organized by: Eurasia Web
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Organized by: WRFER
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United States, New York
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Qatar, Al Rayyan
Organized by: United Science Research Society
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International Conference on Recent Advances in **Medical and Health Sciences**
Jan 29, 2025
China, Beijing
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International Conference on Recent Advances in **Medical and Health Sciences**
Jan 30, 2025
Canada, Vancouver
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International Conference on **Nursing and Healthcare**
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United States, California
Organized by: Japanese Society for Academic Research and Publication
Email: info.jsarap@gmail.com

International Conference on **Healthcare and Clinical Gerontology**
Jan 30, 2025
Germany, Berlin
Organized by: Sciencefora
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International Conference on **Tissue Science and Regenerative Medicine**
Jan 31, 2025
France, Paris
Organized by: aserd.org
Email: info.aserd@gmail.com

International Conference on **Bioinformatics, Biomedicine, Biotechnology and Computational Biology**
Feb 01, 2025
Spain, Seville
Organized by: Eurasia Web
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The 20th International Pan Arab **Critical Care Medicine** Society Conference
Feb 1-3, 2025
Kuwait, Kuwait city
Organized by: Kuwait Critical Care Society

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Feb 03, 2025
United Arab Emirates, Dubai
Organized by: WRFER
Email: contact.wrfer@gmail.com

International Conference on **Medical and Health Sciences**
Feb 04, 2025
Germany, Frankfurt
Organized by: ISERD
Email: info@iserd.co

Kuwait Annual **Radiology** Conference 2025
Feb 6-8, 2025
Kuwait, The Regency Hotel
Organized by: Council of Radiology and Radiation Therapy
Website: kuwaitradiologyconf2025.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Feb 07, 2025
United States, Santa Clara, California
Organized by: WRFER
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International Conference on **Medical & Health Science**
Feb 08, 2025
Uzbekistan, Tashkent
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New Zealand, Christchurch
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Feb 09, 2025
Japan, Nagoya
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International Conference on **Epidemiology & Public Health**
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Australia, Hobart
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Singapore, Singapore
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WHO-Facts Sheet

1. Bipolar disorder
2. Deafness and hearing loss
3. Influenza (seasonal)
4. Measles
5. Podoconiosis

Compiled and edited by
Vineetha E Mammen

Kuwait Medical Journal 2024; 56 (4): 363 - 373

1. Bipolar disorder

KEY FACTS

- Bipolar disorder is a mental health condition that affects a person's mood, energy, activity and thought and is characterized by manic (or hypomanic) and depressive episodes.
- An estimated 40 million people live with bipolar disorder worldwide.
- Bipolar disorder is associated with significant disability and difficulties in many areas of life.
- Many people with bipolar disorder are misdiagnosed or untreated and experience discrimination and stigma.
- There are a range of effective care options, which combine medicines and psychosocial interventions to help people with bipolar disorder stay well.

Overview

In 2019, approximately 1 in 150 adults (40 million people, or 0.53% of the global population) were living with bipolar disorder (1). The condition is primarily observed among working-age people, but also in youth. While the prevalence of bipolar disorder among men and women is approximately equal, available data indicate that women are more often diagnosed.

Worldwide, the treatment coverage for people with bipolar disorder is low. Both men and women are often misdiagnosed. Many lack access to services and recommended interventions, especially in low- and middle-income countries (LMICs).

Stigma and discrimination against people with bipolar disorder are widespread, both in communities and health services. This can undermine access to health care. It also fuels social exclusion and can limit opportunities for education, employment and housing.

Bipolar disorder is one of the leading causes of disability globally as it can affect many areas of life. People with bipolar disorder may experience strained relationships, problems at school or work, and difficulties in carrying out daily activities. Having bipolar disorder also increases the risk of suicide and of developing anxiety and substance use disorders.

People with bipolar disorder are more likely to smoke, use alcohol, have a physical health condition (e.g. cardiovascular or respiratory disease), and experience difficulties in accessing health care. On average, people with bipolar disorder die more than 10 years earlier than the general population (2).

Symptoms and patterns

Bipolar disorder is a mental health condition characterized by mood swings from one extreme to another.

During a manic episode, a person experiences an extremely high mood with lots of energy (feeling very happy, excited, overactive). They may have a sense of euphoria, sudden shifts in mood or an excess of emotion (uncontrollable laughing or feeling much more irritable, agitated or restless than usual).

In manic episodes, the changes in mood and activities are accompanied by other characteristic symptoms, which may include:

- highly inflated sense of self-worth or self-esteem;
- talking quickly and rapidly shifting from one idea to the next;
- having trouble concentrating and being easily distracted;
- decreased need for sleep;
- reckless or risk-taking behaviour, for example overspending, risky sexual activity, drinking, or harming oneself or others; and

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- fixed and mistaken grandiose or persecutory beliefs in something untrue (e.g. "I am a very famous person", "My neighbour is spying on me").

On the contrary, during a depressive episode, a person experiences a depressed mood (feeling sad, irritable, empty). They may feel a loss of interest or pleasure in activities that they had previously enjoyed.

Other symptoms are also present, which may include:

- poor concentration
- feelings of excessive guilt or low self-worth
- hopelessness about the future
- thoughts about dying or suicide
- disrupted sleep
- changes in appetite or weight
- feeling very tired or low in energy.

A depressive episode is different from mood fluctuations commonly experienced by most people, in that the symptoms last most of the day, nearly every day, for at least two weeks.

Both manic and depressive episodes can cause significant difficulties in all aspects of life, including at home, work and school. They may require specialized care to prevent the person from doing harm to themselves or others.

Some people with bipolar disorder may experience what are called hypomanic episodes. Hypomanic episodes involve similar symptoms to manic episodes, but the symptoms are less intense and do not typically disrupt the person's ability to function to the same extent.

There are two main types of bipolar disorder, depending on patterns of manic or hypomanic and depressive episodes.

- People with bipolar type I disorder experience one or more manic episodes interspaced with episodes of depression which usually become more common over time (compared with manic episodes).
- People with bipolar type II disorder have had one or more hypomanic episodes and at least one depressive episode, but no history of manic episodes.

Risks and protective factors

The exact cause of bipolar disorder is unknown. Several factors – including biological (e.g. genetic), psychological, social and structural factors – may contribute to its onset, trajectory and outcomes.

Adverse circumstances or life-altering events can trigger or exacerbate the symptoms of bipolar disorder. These may include bereavement, violence or the breakdown of a relationship. The use of alcohol or drugs can also influence the onset and trajectory of bipolar disorder.

Although employment can be a source of stress for people living with bipolar disorder, it can also be protective. Under good working conditions, and when supported at their workplace with reasonable adjustments, employment can promote recovery by improving functioning, reducing symptoms and leading to a higher quality of life and improved self-esteem.

Treatment and care

Even though symptoms often recur, recovery is possible. With appropriate care, people with bipolar disorder can cope with their symptoms and live meaningful and productive lives.

There are a range of effective treatment options, typically a mix of medicines and psychological and psychosocial interventions. Medicines are considered essential for treatment, but themselves are usually insufficient to achieve full recovery. People with bipolar disorder should be treated with respect and dignity and should be meaningfully involved in care choices, including through shared decision-making regarding treatment and care, balancing effectiveness, side-effects and individual preferences.

Medicines

People with bipolar disorder need treatment and care across acute episodes of mania and depression and when indicated, longer-term treatment to prevent relapse.

Mood stabilizers (such as lithium, valproate) and antipsychotics are proven to help manage acute mania. Lithium prescription requires clinical and laboratory monitoring. Girls and women who are pregnant, breastfeeding or have childbearing potential should not use valproate. Lithium and carbamazepine also need to be avoided during pregnancy and breastfeeding whenever possible.

Antidepressants should not be taken during a manic episode and they may be combined with mood stabilizers or antipsychotics during episodes of depression.

Some medicines for bipolar disorder can make people feel sleepy, have involuntary muscle spasms or tremors, or experience metabolic changes (e.g. involving weight gain). These side effects can affect adherence to treatment and should be monitored and managed.

Adults with bipolar disorder who are in complete remission (no symptoms) usually need to continue with mood stabilizers or antipsychotic medicines for at least six months. Those experiencing multiple episodes of mania and depression will usually require longer-term treatment to minimize relapses.

Psychological and psychosocial interventions

People with bipolar disorder can benefit from lifestyle changes involving regular sleep, physical activity, a healthy diet, reduction of stressors, and mood monitoring.

Psychological interventions (e.g. cognitive behavioural therapy, interpersonal therapy, psychoeducation) can effectively reduce depressive symptoms and the possibility of them coming back.

Family psychoeducation can also help families understand and support their loved one better. Support from family and friends is very important. Support groups – where people can receive encouragement, learn coping skills, and share experiences – can be helpful to people with bipolar disorder and their families.

Recovery-oriented psychosocial interventions include supported employment, supported housing, peer support, and social and life skills training. They serve to promote hope and to support the autonomy, personal empowerment and social inclusion of people with bipolar disorder.

Medicines and psychological or psychosocial interventions should be tailored to the needs of the person and combined for best outcomes.

WHO response

The Comprehensive Mental Health Action Plan 2013-2030 highlights the steps needed to provide appropriate services for people with mental health conditions, including bipolar disorder. The WHO Special Initiative for Mental Health aims to further progress towards the plan's objectives by ensuring 100 million more people can access quality and affordable care for mental health conditions.

WHO's Mental Health Gap Action Programme (mhGAP), which is being implemented in more than 100 countries, provides evidence-based technical guidance, tools and training packages to build capacities and expand treatment coverage for a set of priority conditions, including bipolar disorder, in non-specialized settings in LMICs.

WHO's guidelines on Management of physical health conditions in adults with severe mental disorders provide evidence-based recommendations to practitioners on how to recognize and manage comorbid physical and mental health conditions, including bipolar disorder.

WHO's QualityRights initiative aims to improve the quality of care and human rights standards in mental health and social care facilities and to empower organizations to advocate for the health of people with mental health conditions, including bipolar disorder.

The Guidance on community mental health services and person-centred and rights-based approaches describes what person-centred and human rights-based approaches look like in mental health, and give examples of good practice services.

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2. Kwun Nam Chan J, Ho Yi Yong C, Sau Man Wong C, Yu Hai Chen E, Chung Chang W. Life expectancy and years of potential life lost in bipolar disorder: systematic review and meta-analysis. Br J Psychiatry. 2022;221(3):567–76. doi:10.1192/bjp.2022.19.

2. Deafness and hearing loss

KEY FACTS

- By 2050, nearly 2.5 billion people are projected to have some degree of hearing loss, and at least 700 million will require hearing rehabilitation.
- Over 1 billion young adults are at risk of permanent, avoidable hearing loss due to unsafe listening practices.
- An annual additional investment of less than US$ 1.40 per person is needed to scale up ear and hearing care services globally.
- Over a 10-year period, this promises a return of nearly US$ 16 for every US dollar invested.

Overview

Over 5% of the world's population – or 430 million people – require rehabilitation to address their disabling hearing loss (including 34 million children). It is estimated that by 2050 over 700 million people – or 1 in every 10 people – will have disabling hearing loss.

Disabling hearing loss refers to hearing loss greater than 35 decibels (dB) in the better hearing ear. Nearly 80% of people with disabling hearing loss live in low- and middle-income countries. The prevalence of hearing loss increases with age, among those older than 60 years, over 25% are affected by disabling hearing loss.

Hearing loss and deafness

A person who is not able to hear as well as someone with normal hearing – hearing thresholds of 20 dB or better in both ears – is said to have hearing loss. Hearing

loss may be mild, moderate, severe or profound. It can affect one ear or both ears and leads to difficulty in hearing conversational speech or loud sounds.

Hard of hearing refers to people with hearing loss ranging from mild to severe. People who are hard of hearing usually communicate through spoken language and can benefit from hearing aids, cochlear implants, and other assistive devices as well as captioning.

Deaf people mostly have profound hearing loss, which implies very little or no hearing. They often use sign language for communication.

Causes of hearing loss and deafness

Although these factors can be encountered at different periods across the life span, individuals are most susceptible to their effects during critical periods in life.

Prenatal period

- genetic factors including hereditary and non-hereditary hearing loss
- intrauterine infections – such as rubella and cytomegalovirus infection.

Perinatal period

- birth asphyxia (a lack of oxygen at the time of birth
- hyperbilirubinemia (severe jaundice in the neonatal period)
- low-birth weight
- other perinatal morbidities and their management.

Childhood and adolescence

- chronic ear infections (chronic suppurative otitis media)
- collection of fluid in the ear (chronic nonsuppurative otitis media)
- meningitis and other infections.

Adulthood and older age

- chronic diseases
- smoking
- otosclerosis
- age-related sensorineural degeneration
- sudden sensorineural hearing loss.

Factors across the life span

- cerumen impaction (impacted ear wax)
- trauma to the ear or head
- loud noise/loud sounds
- ototoxic medicines
- work related ototoxic chemicals
- nutritional deficiencies
- viral infections and other ear conditions
- delayed onset or progressive genetic hearing loss.

The impact of unaddressed hearing loss

When unaddressed, hearing loss impacts many aspects of life at individual level:

- communication and speech;
- cognition;
- social isolation, loneliness and stigma;
- impact on society and economy;effects on years lived with disability (YDLs) and disability adjusted life years (DALYs); and
- education and employment: In developing countries, children with hearing loss and deafness often do not receive schooling. Adults with hearing loss also have a much higher unemployment rate. Among those who are employed, a higher percentage of people with hearing loss are in the lower grades of employment compared with the general workforce.

WHO estimates that unaddressed hearing loss poses an annual global cost of US$ 980 billion. This includes health sector costs (excluding the cost of hearing devices), costs of educational support, loss of productivity and societal costs. Of these costs, 57% are attributed to low- and middle-income countries.

Prevention

Many of the causes that lead to hearing loss can be avoided through public health strategies and clinical interventions implemented across the life course.

Prevention of hearing loss is essential throughout the life course, from prenatal and perinatal periods to older age. In children, nearly 60% of hearing loss is due to avoidable causes that can be prevented through implementation of public health measures. Likewise, most common causes of hearing loss in adults, such as exposure to loud sounds and ototoxic medicines, are preventable.

Effective strategies for reducing hearing loss at different stages of the life course include:

- immunization;
- good maternal and childcare practices;
- genetic counselling;
- identification and management of common ear conditions;
- occupational hearing conservation programmes for noise and chemical exposure;
- safe listening strategies for the reduction of exposure to loud sounds in recreational settings; and
- rational use of medicines to prevent ototoxic hearing loss.

Identification and management

Early identification of hearing loss and ear diseases is key to effective management. This requires systematic screening for detection of hearing loss and related ear diseases in those who are most at risk. This includes:

- newborn babies and infants
- pre-school and school-age children
- people exposed to noise or chemicals at work
- people receiving ototoxic medicines
- older adults.

Hearing assessment and ear examination can be conducted in clinical and community settings. Tools such as the hearWHO app and other technology-based solutions make it possible to screen for ear diseases and hearing loss with limited training and resources.

Once hearing loss is identified, it is essential that it is addressed as early as possible and in an appropriate manner, to mitigate any adverse impact.

Rehabilitation for hearing loss

Rehabilitation helps people with hearing loss to function at their optimum, which means they can be as independent as possible in everyday activities. Specifically, rehabilitation helps them to participate in education, work, recreation and meaningful roles, e.g. in their families or communities–throughout their lives. Interventions for rehabilitation for people with hearing loss include:

- the provision of, and training in the use of, hearing technologies (e.g. hearing aids, cochlear implants and middle ear implants);
- speech and language therapy to enhance perceptive skills and develop communication and linguistic abilities; training in the use of sign language and other means of sensory substitution (e.g. speech reading, use of print on palm, Tadoma, signed communication);
- the provision of hearing assistive technology, and services (e.g. frequency modulation and loop systems, alerting devices, telecommunication devices, captioning services and sign language interpretation); and
- counselling, training and support to enhance engagement in education, work and community life.

WHO response

WHO's work on ear and hearing care is to promote integrated people-centred ear and hearing care (IPC-EHC).

WHO's work is guided by the recommendations of the WHO World report on hearing (2021) and the World Health Assembly resolution on prevention of deafness and hearing loss.

WHO's work includes:

- guiding, assisting and supporting Member States to increase awareness of ear and hearing care issues;
- facilitating data generation and dissemination of ear and hearing care-related data and information, such as through the World report on hearing;
- providing technical resources and guidance to facilitate planning and health systems capacity building for ear and hearing care;
- providing guidance to strengthen rehabilitation for people with hearing loss through the Package of interventions for rehabilitation for hearing loss;
- supporting health workforce training in ear and hearing care through the Primary ear and hearing care training resources;
- promoting safe listening to reduce the risk of recreational noise-induced hearing loss through the WHO Make Listening Safe initiative;
- observing and promoting World Hearing Day as an annual advocacy event;
- building partnerships to develop strong hearing care programmes, including initiatives for including affordable and accessible ear and hearing care services and hearing aids in service delivery approaches suitable for low-and middle-income countries and cochlear implants; and
- advocating for ear and hearing care through the World Hearing Forum.

3. Influenza (seasonal)

KEY FACTS

- There are around a billion cases of seasonal influenza annually, including 3–5 million cases of severe illness.
- It causes 290 000 to 650 000 respiratory deaths annually.
- Ninety-nine percent of deaths in children under 5 years of age with influenza-related lower respiratory tract infections are in developing countries.
- Symptoms begin 1–4 days after infection and usually last around a week.

Overview

Seasonal influenza (the flu) is an acute respiratory infection caused by influenza viruses. It is common in all parts of the world. Most people recover without treatment.

Influenza spreads easily between people when they cough or sneeze. Vaccination is the best way to prevent the disease.

Symptoms of influenza include acute onset of fever, cough, sore throat, body aches and fatigue. Treatment should aim to relieve symptoms. People with the flu should rest and drink plenty of liquids. Most peple will recover on their own within a week. Medical care may be needed in severe cases and for people with risk factors.

There are 4 types of influenza viruses, types A, B, C and D. Influenza A and B viruses circulate and cause seasonal epidemics of disease.

- Influenza A viruses are further classified into subtypes according to the combinations of the proteins on the surface of the virus. Currently circulating in humans are subtype A(H1N1) and A(H3N2) influenza viruses. The A(H1N1) is also written as A(H1N1)pdm09 as it caused the pandemic in 2009 and replaced the previous A(H1N1) virus which had circulated prior to 2009. Only influenza type A viruses are known to have caused pandemics.
- Influenza B viruses are not classified into subtypes but can be broken down into lineages. Influenza type B viruses belong to either B/Yamagata or B/Victoria lineage.
- Influenza C virus is detected less frequently and usually causes mild infections, thus does not present public health importance.
- Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people.

Signs and symptoms

Symptoms of influenza usually begin around 2 days after being infected by someone who has the virus.

Symptoms include:

- sudden onset of fever
- cough (usually dry)
- headache
- muscle and joint pain
- severe malaise (feeling unwell)
- sore throat
- runny nose.

The cough can be severe and can last 2 weeks or more. Most people recover from fever and other symptoms within a week without requiring medical attention. However, influenza can cause severe illness or death, especially in people at high risk.

Influenza can worsen symptoms of other chronic diseases. In severe cases influenza can lead to pneumonia and sepsis. People with other medical issues or who have severe symptoms should seek medical care.

Hospitalization and death due to influenza occur mainly among high-risk groups. In industrialized countries most deaths associated with influenza occur among people aged 65 years or older (1).

The effects of seasonal influenza epidemics in developing countries are not fully known, but research estimates that 99% of deaths in children under 5 years of age with influenza related lower respiratory tract infections are in developing countries (2).

Epidemiology

All age groups can be affected but there are groups that are more at risk than others.

- People at greater risk of severe disease or complications when infected are pregnant women, children under 5 years of age, older people, individuals with chronic medical conditions (such as chronic cardiac, pulmonary, renal, metabolic, neurodevelopmental, liver or hematologic diseases) and individuals with immunosuppressive conditions/treatments (such as HIV, receiving chemotherapy or steroids, or malignancy).
- Health and care workers are at high risk of acquiring influenza virus infection due to increased exposure to the patients, and of further spreading particularly to vulnerable individuals. Vaccination can protect health workers and the people around them.

Epidemics can result in high levels of worker/school absenteeism and productivity losses. Clinics and hospitals can be overwhelmed during peak illness periods.

Transmission

Seasonal influenza spreads easily, with rapid transmission in crowded areas including schools and nursing homes. When an infected person coughs or sneezes, droplets containing viruses (infectious droplets) are dispersed into the air and can infect persons in close proximity. The virus can also be spread by hands contaminated with influenza viruses. To prevent transmission, people should cover their mouth and nose with a tissue when coughing and wash their hands regularly.

In temperate climates, seasonal epidemics occur mainly during winter, while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly.

The time from infection to illness, known as the incubation period, is about 2 days, but ranges from 1–4 days.

Diagnosis

Most cases of human influenza are clinically diagnosed. However, during periods of low influenza activity or outside of epidemics situations, the infection of other respiratory viruses (e.g. SARS-CoV-2, rhinovirus, respiratory syncytial virus, parainfluenza and adenovirus) can also present as influenza-like illness (ILI), which makes the clinical differentiation of influenza from other pathogens difficult.

Collection of appropriate respiratory samples and the application of a laboratory diagnostic test is required to establish a definitive diagnosis. Proper collection, storage and transport of respiratory specimens is the essential first step for laboratory detection of influenza virus infections. Laboratory confirmation is commonly performed using direct antigen detection, virus isolation, or detection of influenza-specific RNA by reverse transcriptase-polymerase chain reaction (RT-PCR). Various guidance on the laboratory techniques is published and updated by WHO.

Rapid diagnostic tests are used in clinical settings, but they have lower sensitivity compared to RT-PCR methods and their reliability depends largely on the conditions under which they are used.

Treatment

Most people will recover from influenza on their own. People with severe symptoms or other medical conditions should seek medical care.

People with mild symptoms should:

- stay home to avoid infecting other people
- rest
- drink plenty of fluids
- treat other symptoms such as fever
- seek medical care if symptoms get worse.

People at high risk or with severe symptoms should be treated with antiviral medications as soon as possible.

They include people who are:

- pregnant
- children under 59 months of age
- aged 65 years and older
- living with other chronic illnesses
- receiving chemotherapy
- living with suppressed immune systems due to HIV or other conditions.

The WHO Global Influenza Surveillance and Response System (GISRS) monitors resistance to antivirals among circulating influenza viruses to provide timely evidence for national policies related to antiviral use.

Prevention

Vaccination is the best way to prevent influenza. Safe and effective vaccines have been used for more than 60 years. Immunity from vaccination goes away over time so annual vaccination is recommended to protect against influenza.

The vaccine may be less effective in older people, but it will make the illness less severe and reduces the chance of complications and death.

Vaccination is especially important for people at high risk of influenza complications and their carers.

Annual vaccination is recommended for:

- pregnant women
- children aged 6 months to 5 years
- people over age 65
- people with chronic medical conditions
- health workers.

Other ways to prevent influenza:

- wash and dry your hands regularly
- cover your mouth and nose when coughing or sneezing
- dispose of tissues correctly
- stay home when feeling unwell
- avoid close contact with sick people
- avoid touching your eyes, nose or mouth.

Vaccines

Vaccines are updated routinely with new vaccines developed that contain viruses that match those circulating. Several inactivated influenza vaccines and recombinant influenza vaccines are available in injectable form. Live attenuated influenza vaccines are available as a nasal spray.

WHO response

WHO, through the Global Influenza Programme and GISRS, in collaboration with other partners, continuously monitors influenza viruses and activity globally, recommends seasonal influenza vaccine compositions twice a year for the northern and southern hemisphere influenza seasons, guides countries in tropical and subtropical areas as to which formulation vaccines to use, supports decisions for timing of vaccination campaigns, and supports Member States to develop prevention and control strategies.

WHO works to strengthen national, regional and global influenza response capacities including diagnostics, antiviral susceptibility monitoring, disease surveillance and outbreak response, to increase vaccine coverage among high-risk groups, and to support research and development of new therapeutics and other countermeasures.

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4. Measles

KEY FACTS

- Measles is a highly contagious, serious airborne disease caused by a virus that can lead to severe complications and death.
- Measles vaccination averted 57 million deaths being between 2000 and 2022.
- Even though a safe and cost-effective vaccine is available, in 2022, there were an estimated 136 000 measles deaths globally, mostly among unvaccinated or under vaccinated children under the age of 5 years.
- The proportion of children receiving a first dose of measles vaccine was 83% in 2023, well below the 2019 level of 86%.

Overview

Measles is a highly contagious disease caused by a virus. It spreads easily when an infected person breathes, coughs or sneezes. It can cause severe disease, complications, and even death. Measles can affect anyone but is most common in children. Measles infects the respiratory tract and then spreads throughout the body. Symptoms include a high fever, cough, runny nose and a rash all over the body.

Being vaccinated is the best way to prevent getting sick with measles or spreading it to other people. The vaccine is safe and helps your body fight off the virus.

Before the introduction of measles vaccine in 1963 and widespread vaccination, major epidemics occurred approximately every two to three years and caused an estimated 2.6 million deaths each year.

An estimated 136 000 people died from measles in 2022 – mostly children under the age of five years, despite the availability of a safe and cost-effective vaccine.

Accelerated immunization activities by countries, WHO, the Measles & Rubella Partnership (formerly the Measles & Rubella Initiative), and other international partners successfully prevented an estimated 57 million deaths between 2000–2022. Vaccination decreased an estimated measles deaths from 761 000 in 2000 to 136 000 in 2022 (1).

Effects of the COVID-19 pandemic

The COVID-19 pandemic led to setbacks in surveillance and immunization efforts. The suspension of immunization services and declines in immunization rates and surveillance across the globe left millions of children vulnerable to preventable diseases like measles.

No country is exempt from measles, and areas with low immunization encourage the virus to circulate, increasing the likelihood of outbreaks and putting all unvaccinated children at risk.

We must regain progress and achieve regional measles elimination targets, despite the COVID-19 pandemic. Immunization programs should be strengthened within primary healthcare, so efforts to reach all children with two measles vaccine doses should be accelerated. Countries should also implement robust surveillance systems to identify and close immunity gaps.

Signs and symptoms

Symptoms of measles usually begin 10–14 days after exposure to the virus. A prominent rash is the most visible symptom.

Early symptoms usually last 4–7 days. They include:

- running nose
- cough
- red and watery eyes
- small white spots inside the cheeks.

The rash begins about 7–18 days after exposure, usually on the face and upper neck. It spreads over about 3 days, eventually to the hands and feet. It usually lasts 5–6 days before fading. Most deaths from measles are from complications related to the disease.

Complications can include:

- blindness
- encephalitis (an infection causing brain swelling and potentially brain damage)
- severe diarrhoea and related dehydration
- ear infections
- severe breathing problems including pneumonia.

If a woman catches measles during pregnancy, this can be dangerous for the mother and can result in her baby being born prematurely with a low birth weight.

Complications are most common in children under 5 years and adults over age 30. They are more likely in children who are malnourished, especially those without enough vitamin A or with a weak immune system from HIV or other diseases. Measles itself also weakens the immune system and can make the body "forget" how to protect itself against infections, leaving children extremely vulnerable.

Who is at risk?

Any non-immune person (not vaccinated or vaccinated but did not develop immunity) can become infected. Unvaccinated young children and pregnant persons are at highest risk of severe measles complications.

Measles is still common, particularly in parts of Africa, the Middle East and Asia. The overwhelming majority of measles deaths occur in countries with low per capita incomes or weak health infrastructures that struggle to reach all children with immunization.

Damaged health infrastructure and health services in countries experiencing or recovering from a natural disaster or conflict interrupt routine immunization and overcrowding in residential camps increases the risk of infection. Children with malnutrition or other causes of a weak immune system are at highest risk of death from measles.

Transmission

Measles is one of the world's most contagious diseases, spread by contact with infected nasal or throat secretions (coughing or sneezing) or breathing the air that was breathed by someone with measles. The virus remains active and contagious in the air or on infected surfaces for up to two hours. For this reason, it is very infectious, and one person infected by measles can infect nine out of 10 of their unvaccinated close contacts. It can be transmitted by an infected person from four days prior to the onset of the rash to four days after the rash erupts.

Measles outbreaks can result in severe complications and deaths, especially among young, malnourished children. In countries close to measles elimination, cases imported from other countries remain an important source of infection.

Treatment

There is no specific treatment for measles. Caregiving should focus on relieving symptoms, making the person comfortable and preventing complications.

Drinking enough water and treatments for dehydration can replace fluids lost to diarrhoea or vomiting. Eating a healthy diet is also important.

Doctors may use antibiotics to treat pneumonia and ear and eye infections. All children or adults with measles should receive two doses of vitamin A supplements, given 24 hours apart. This restores low vitamin A levels that occur even in well-nourished children. It can help prevent eye damage and blindness. Vitamin A supplements may also reduce the number of measles deaths.

Prevention

Community-wide vaccination is the most effective way to prevent measles. All children should be vaccinated against measles. The vaccine is safe, effective and inexpensive.

Children should receive two doses of the vaccine to ensure they are immune. The first dose is usually given at 9 months of age in countries where measles is common and 12–15 months in other countries. A second dose should be given later in childhood, usually at 15–18 months.

The measles vaccine is given alone or often combined with vaccines for mumps, rubella and/or varicella.

Routine measles vaccination, combined with mass immunization campaigns in countries with high case rates are crucial for reducing global measles deaths. The measles vaccine has been in use for about 60 years and costs less than US$ 1 per child. The measles vaccine is also used in emergencies to stop outbreaks from spreading. The risk of measles outbreaks is particularly high amongst refugees, who should be vaccinated as soon as possible.

Combining vaccines slightly increases the cost but allows for shared delivery and administration costs and importantly, adds the benefit of protection against rubella, the most common vaccine preventable infection that can infect babies in the womb.

In 2023, 74% of children received both doses of the measles vaccine, and about 83% of the world's children received one dose of measles vaccine by their first birthday. Two doses of the vaccine are recommended to ensure immunity and prevent outbreaks, as not all children develop immunity from the first dose.

Approximately 22 million infants missed at least one dose of measles vaccine through routine immunization in 2023.

WHO response

In 2020, WHO and global stakeholders endorsed the Immunization Agenda 2021–2030. The Agenda aims to achieve the regional targets as a core indicator of impact, positioning measles as a tracer of a health system's ability to deliver essential childhood vaccines.

WHO published the Measles and rubella strategic framework in 2020, establishing seven necessary strategic priorities to achieve and sustain the regional measles and rubella elimination goals.

During 2000–2022, supported by the Measles & Rubella Initiative (now the Measles and Rubella Partnership) and Gavi, measles vaccination prevented an estimated 57 million deaths; mostly

in the WHO African Region and Gavi-supported countries.

Without sustained attention, hard-fought gains can easily be lost. Where children are unvaccinated, outbreaks occur. Based on current trends of measles vaccination coverage and incidence, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) concluded that measles elimination is under threat, as the disease resurged in numerous countries that achieved, or were close to achieving, elimination.

WHO continues to strengthen the Global Measles and Rubella Laboratory Network (GMRLN) to ensure timely diagnosis of measles and track the virus' spread to assist countries in coordinating targeted vaccination activities and reduce deaths from this vaccine-preventable disease.

The IA2030 Measles & Rubella Partnership

The Immunization Agenda 2030 Measles & Rubella Partnership (M&RP) is a partnership led by the American Red Cross, United Nations Foundation, Centers for Disease Control and Prevention (CDC), Gavi, the Vaccines Alliance, the Bill and Melinda French Gates Foundation, UNICEF and WHO, to achieve the IA2030 measles and rubella specific targets. Launched in 2001, as the Measles and Rubella Initiative, the revitalized Partnership is committed to ensuring no child dies from measles or is born with congenital rubella syndrome. The Partnership helps countries plan, fund and measure efforts to permanently stop measles and rubella

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5. Podoconiosis

KEY FACTS

- Podoconiosis affects an estimated 4 million people across 17 countries worldwide.
- Podoconiosis affects people of all ages and genders, but women and girls are disproportionately impacted.
- Podoconiosis causes avoidable disability through swollen, deformed feet and lower legs and painful acute attacks that render patients bedbound for 3–5 days each episode.
- Prevention is through avoiding contact with irritant soil by wearing footwear, covering house floors and paving roads.
- Treatment is low-cost and simple, benefitting the poorest patients the most.

Overview

Podoconiosis is a non-infectious geochemical leg swelling (lymphoedema) caused by long-term exposure of bare feet to irritant soils. It is responsible for an estimated 4 million cases of lymphoedema in highland tropical and sub-tropical areas of 17 countries in Africa, Central and South America and South and South-East Asia.

Podoconiosis affects poor, remote, subsistence farming communities and, by affecting livelihoods, it traps these communities in poverty. Women and girls are both more likely to contract podoconiosis and more likely to suffer from its social and economic consequences.

Interventions include prevention of contact with the soil through consistent wearing of shoes from an early age and daily foot washing. Treatment using a holistic lymphoedema management package has been demonstrated to decrease swelling, disability and incidence of acute attacks, improve quality of life, and can be readily mainstreamed into government community health services.

Scope of the problem

Globally, there is evidence of podoconiosis in 17 countries (12 in Africa, 3 in Latin America and 2 in Asia). Tropical African countries bear the highest disease burden with about 1.5 million people living with podoconiosis in Ethiopia, a further 40 000 in Cameroon, 9000 in Kenya and 7000 in Rwanda.

Who is at risk?

Podoconiosis is common among remote rural communities, in particular those dependent on subsistence farming and lacking access to footwear or water to wash the feet. The average age at first noticing leg swelling is 25 years, and the disease is common up to the sixth decade. The disease is more common in women: a recent meta-analysis concluded that the likelihood of podoconiosis among women was 1.15 times greater than among men.

Signs and symptoms

The early symptoms of podoconiosis include a burning sensation and itching on the back of the feet. Skin thickening is accompanied by papillomatous growths around the sides of the feet and the heel. Reversible foot and lower leg oedema (swelling) later becomes fixed and gradually progresses up the leg. Swelling is bilateral but often asymmetrical and the swelling is mostly limited to below the knees. Nodules and maceration between toes are common.

Causes

Podoconiosis is a condition that is jointly influenced by genetic and environmental factors. No biological agent has been identified. There is an association between podoconiosis and areas of the genome often involved in T-cell mediated inflammatory responses, and an exaggerated helper T-cell response has been demonstrated in the lymph nodes of affected people. Although ecological evidence over several decades has linked red clay soils to podoconiosis, the exact causative agent within the soil remains unknown. Studies have suggested a role for smectite clays or certain elements including zirconium, aluminium and beryllium.

Treatment and care

Treatment of podoconiosis is currently based on lymphoedema management (foot hygiene, compression, exercises and elevation), psychosocial and mental health support, and use of shoes to reduce exposure to irritant soil. Surgical removal of large nodules can be achieved with satisfactory healing rates, allowing patients to use custom designed shoes. The effectiveness and cost-effectiveness of a holistic physical and mental health care package for people with lymphoedema caused by lymphatic filariasis, leprosy or podoconiosis (mainstreamed into routine primary health care services in Ethiopia) has been demonstrated. Expert patients (patients who have been trained to successfully manage their condition and assist others in doing so) can be trained to guide treatment for uncomplicated lymphoedema.

Prevention and control

The key strategies for podoconiosis control are prevention of contact with irritant soil (primary prevention) and lymphoedema morbidity management (secondary and tertiary prevention). Evidence from the past 5 years suggests that podoconiosis is amenable to public health interventions such as footwear and hygiene-based morbidity management, which reduce acute clinical episodes. Controlling podoconiosis is achievable given the absence of a biological agent or vector also needing control, the relatively small global scale of the problem, and the safe means of podoconiosis prevention and control.

Challenges

The main challenge faced in podoconiosis control is lack of awareness that the condition exists and that it is different from lymphatic filariasis and other main causes of lymphoedema in the tropics, requiring different prevention and control strategies. Treatment is most effective when the disease is diagnosed early. Podoconiosis takes longer to identify than it should through lack of diagnostic tools that can be used in the community. There is also a lack of understanding of the exact environmental trigger. Finally, communities affected have little voice at regional or national level, and attention needs to be drawn to the structural inequities that contribute to the persistence of this preventable condition.

Global impact

Until recently, podoconiosis was assumed to lead to illness rather than deaths. However, the death rate among people with podoconiosis is greater than that of a comparison cohort in a similar setting, with an overall standardized mortality rate of 6. Podoconiosis also has severe social and economic consequences. Patients lose 45% of their economically productive time because of morbidity associated with the disease. In Ethiopia alone, it is estimated that podoconiosis causes 172 073 disability-adjusted life-years (DALYs) to be lost annually. Most of these DALYs are due to chronic lymphoedema, and only 2.6% are attributable to ADLA episodes. Podoconiosis is considered the most stigmatizing health problem in endemic areas. Patients have almost 7 times the risk of lower-than-average quality of life scores and 11 times the likelihood of depression than healthy neighbours.

WHO response

Podoconiosis management and public health control measures can be integrated within the strategic framework for skin-related neglected tropical diseases, and the wider agenda of poverty reduction and Universal Health Coverage.

Reducing the suffering of people affected by podoconiosis will rely on 2 of the public health strategies already recommended by WHO for NTDs:

- Innovative and Intensified Disease Management (IDM). There are many similarities between Morbidity Management and Disability Prevention (MMDP) for podoconiosis and for filarial lymphoedema and leprosy. The effectiveness and cost-effectiveness of integrated care across these three NTDs has been demonstrated.
- Water, sanitation and hygiene (WASH). Access to clean water is essential for prevention of podoconiosis and for MMDP. This requirement is shared with several other NTDs including soil-transmitted helminthiases, schistosomiasis, trachoma and lymphatic filariasis.

Synergies in prevention include promotion of footwear (as for snakebite, soil-transmitted helminth infections, Buruli ulcer, mycetoma and tungiasis) and covering of house floors (as for tungiasis). The inclusion podoconiosis in the skin NTD framework will enhance surveillance and visibility.

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