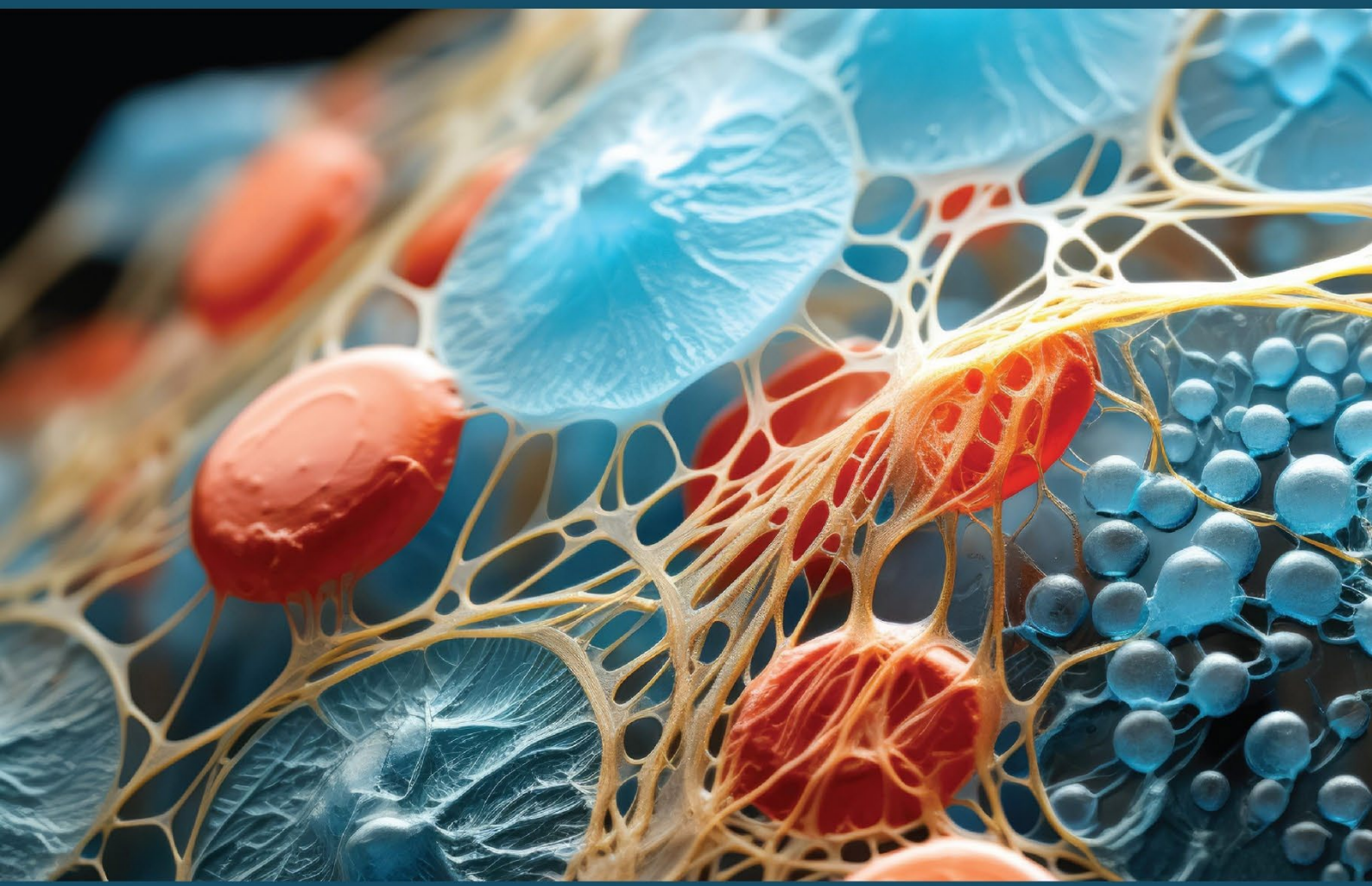
Journal of Clinical and Translational Research



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ABOUT JCTR

Aims and scope

The Journal of Clinical and Translational Research (JCTR) is an open access, peer-reviewed, multidisciplinary scientific journal that publishes studies with at least an ex vivo, in vivo, or clinical component. The published research is centered on any clearly defined clinical problem, which may comprise a disease or the basis of disease, a form of therapy or intervention, and clinical diagnostics or prognostics. Articles (original research, reviews, technical reports, medical hypotheses, commissioned articles, special issue articles, and editorials) are published continuously online and bimonthly in print. Studies performed in cells only will generally not be accepted unless they contain critical data that are in line with the scope of the journal. Some examples of such studies include molecular pathways that lie at the basis of a disease, novel biotechnological approaches for e.g., the production of drugs, or new techniques that improve clinical diagnostics and prognostics. Articles that combine preclinical and clinical data are given priority. Contributions from academic institutions and industry are welcome.

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REVIEW ARTICLE

Tissue engineering and regenerative medicine in otorhinolaryngology

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Abstract:

Background and Aim: Regenerative medicine has been gaining popularity in the field of medicine, and the possibilities for tissue regeneration are immense in the field of otorhinolaryngology, which involves sensory organs and vital functions such as breathing and swallowing. Regenerative strategies offer the potential to restore functions such as hearing, facial expression, olfaction, and speaking, thereby reducing the disadvantages and risks related to traditional reconstruction strategies. This review summarizes the progress of regenerative medicine in otology and hearing, laryngeal surgery, rhinology, and craniofacial reconstruction.
Relevance for Patients: Patients can be informed about the progress of regenerative medicine in the field of otorhinolaryngology and how it has evolved to ameliorate the symptoms of common diseases or cure even more severe ones.

1. Introduction

Over the past decade, regenerative medicine and tissue engineering have gained popularity in the medical and pharmaceutical sectors, owing to the ability of tissue engineering to correct medical defects using scaffolds that mimic the natural form and function of many organs and tissues. Regenerative medicine can also be applied in the field of otorhinolaryngology to treat common anatomical and physiological deficiencies. These deficiencies are congenital by nature or can develop from head and neck cancer treatment (e.g., radiotherapy and surgery). Tissue replacement, using grafts derived from other tissues and artificial materials, is a traditional approach to addressing these deficiencies [1].

Cells, biocompatible scaffolds, and bioactive factors are the three major types of treatment used in regenerative medicine (Table 1) [2,3]. Cells, including stem, progenitor, or differentiated cells, can be employed to rebuild tissues and alter the immune response and cell behavior [4]. Scaffolds, synthetic or biological, are 3D structures designed to fit into defects and restore the diseased organs' function. They can be combined with bioactive factors or cell components to control differentiation and migration to specified tissues [5]. *In vivo*, the cell processes involved in cell regeneration can be influenced by various molecules, including growth factors, cytokines, hormones, and other compounds [6,7]. In addition, these strategies have disadvantages, such as the requirement of immunosuppressive drugs, donor site morbidity, infection, and rejection risks [8]. Whilst the transplantation of bioengineered tissues can overcome the latter hindering factors, extensive trials to overcome the bio-ethical challenges are necessary to significantly improve the use of regenerative tissue medicine in the field of otorhinolaryngology.

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Table 1. Tissue engineering and regenerative medicine concepts

Stem cells			Bioactive factors	Scaffolds	
Totipotent stem cells	**Pluripotent stem cells**	**Multipotent stem cells**		**Biological material**	**Synthetic material**
Differentiate into embryonic and extra-embryonic tissues	Differentiate into the entire range of derivatives of all three embryonic germ layers	Differentiate into derivatives of multiple cell lineages	Cytokines, growth factors, hormones, and morphogenic proteins	Trachea and aortic allograft	Ceramic, metal, polymer, and composite
Obtained from an early embryo in the two-cell stage	Includes ESC and iPSC	Includes NSCs and MSCs from the bone marrow, fat, skin, umbilical cord, and/or muscle			

Abbreviations: ESC: Embryonic stem cell; NSCs: Neural stem cells; MSCs: Mesenchymal stem cells; iPSC: induced pluripotent stem cell.

The field of otorhinolaryngology is extensive, including many different tissues and functions such as hearing, balance, olfaction, facial expression, breathing, and speaking. The diverse cells and tissues in the ear, nose, and throat, which are responsible for the related vital functions, contribute to the heterogeneity challenging the exploitation of regenerative therapies. This review aims to narratively summarize the current state of tissue engineering and regenerative medicine in otorhinolaryngology.

2. Methods

This paper provides a literature overview of regenerative medicine and tissue engineering in otorhinolaryngology. A literature search was conducted in PubMed, CINAHL, and Scopus using the following terms: "regenerative medicine," "tissue engineering," "regenerative surgery," "stem cells," "ear," "cochlea," "hearing loss," "nose," "larynx," "head and neck," "vocal fold," "trachea," "craniofacial," "otology," "rhinology," "laryngology," "salivary glands," and "otorhinolaryngology," from database inception to 2022. We used Boolean operators to refine our search. In addition, review articles from the reference list were included.

All randomized and non-randomized controlled prospective and retrospective trials and case series of two or more patients of any age were included. Only articles written in English were further considered for the study. Duplicates were excluded. Articles related to oral surgery and maxillofacial surgery were excluded. Although randomized controlled trials were prioritized and human clinical trials were preferred, animal trials were also reviewed and included. Most articles were pre-clinical animal studies, reflecting the current state of research on this topic. Information from completed early-phase clinical trials was included, while ongoing clinical trials were excluded. Articles were analyzed and selected based on relevance to the topic of interest.

3. Results

The literature search identified 622 studies, of which 105 fit the eligibility criteria for data curation. Forty studies reported on otology and hearing, eight on craniofacial cartilaginous reconstruction, four on salivary glands, and 46 on laryngology.

4. Applications in Otology and Hearing

4.1. Cochlea

Loss of hearing, congenital or acquired, results in the hair cells' inability to function correctly and subsequent death [9]. The absence of hair cells causes the death of spiral ganglion neurons (SGNs) [9]. The mature mammalian cochlea in mammals is incapable of hair cell regeneration [10]. Intracellular stem cell activation and external stem cell transplantation are two approaches in regenerative medicine that can potentially treat sensorineural hearing loss. The first approach is to stimulate the stem cells present in the organ of Corti, leading to the replacement of damaged hair cells. The second technique involves introducing stem cells from an external source into the inner ear. Several papers reported using mesenchymal stem cells (MSCs) in animal models with hearing loss (Table 2). The injection of primary MSCs into the cochlea may result in the survival of hair cells [9]. However, there is currently minimal indication of the transdifferentiation of MSCs into hair-like cells or neurons *in vivo* [9].

Jang *et al.* implanted human bone marrow MSCs (BM-MSCs) into the cochlea of neomycin-deafened guinea pigs, resulting in a more significant number of SGNs as compared to the control group [11]. MSCs have also been utilized in human research but with minimal hearing enhancement [12]. In 2015, a clinical experiment explored the efficacy of transplanting autologous BM-MSCs in patients with sensorineural hearing loss. Two individuals were intravenously injected with cells, but their hearing did not improve [12]. Eleven children participated in another clinical trial using an autologous umbilical cord stem cell infusion [13]. There were no adverse events reported, and significant improvement in hearing was discovered from several hearing tests.

It is more difficult to regenerate the auditory nerve using stem cell technology due to the electrical features of those cells and the requirement for an adequate connection with the remaining residual auditory neurons [14]. *In vitro* studies have revealed that MSCs obtained from the olfactory mucosa can stimulate the myelination of oligodendrocytes [9]. However, an ideal transplantation method has not been established thus far. Systemic injection, injection into the scala tympani via the round window or a basal turn cochleostomy, and injection into the scala media are some of the stem cell transfer methods for the cochlea [14].

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Table 2. Animal model studies on MSCs in hearing loss

Study	Cell type	Method	Model	Results
Pandit *et al*., 2011 [20]	Human OSCs	Injection of OSCs into the cochlea through lateral cochleostomy	Mice	The hearing thresholds were substantially lower in the experimental group as compared to the control group. There was no integration of transplanted cells into cochlear tissues.
Choi *et al*., 2012 [21]	Human BM-MSCs	Intravenous injection of MSCs	Rats	Most of the injected MSCs were located in the lungs and a small number were in the spiral ganglion region.
Kasagi *et al*., 2013 [22]	Mouse MSCs	Infusion of MSCs into the ampulla of SCC	Mice	MSCs moved to the cochlea and differentiated into fibrocytes. The auditory brainstem response (ABR) did not alter in the experimental group compared to the control group.
Bas *et al*., 2014 [23]	Human olfactory MSC-like stem cells	Applied MSCs to cochlear cultures	Rats	The spiral ganglion neuron population was restored.
Jang *et al*., 2015 [11]	Human bone marrow neural-induced MSCs	hMSCs were transplanted into the scala tympani of damaged cochlea	Guinea pigs	Transplanted hMSCs were found within the perilymphatic space, the organ of Corti, along the cochlear nerve fibers, and in the spiral ganglion. The quantity of SGNs was elevated in comparison to the control group.
Yoo *et al*., 2015 [24]	Human adipose tissue-derived MSCs	Intraperitoneal injection of hMSCs	Mouse model of autoimmune hearing loss	There were improvements in hearing function in the intervention group as compared to the control group.
Xu *et al*., 2016 [25]	Rat olfactory epithelium neural stem cells	Stem cells were injected straight into the cochlea	Rats	There was migration of stem cells around the SGNs, and hearing loss improved as determined by ABR.
Le *et al*., 2017 [26]	Magnetically labeled rat MSCs	MSCs were injected into the systemic circulation	Rats	The presence of MSCs in the cochlea was identified, and the experimental group had a significant increase in hearing threshold levels.
Chen *et al*., 2018 [27]	Human urinary cells reprogrammed into iPSCs	OEPs were produced from iPSCs and transplanted into the cochlea of mice	Mice	A healthy donor's urine cells were converted into iPSCs. These were stimulated to develop into OEPs and hair cell-like cells. Co-cultured hair cell-like cells generated from OEP developed synaptic connections with SGNs in vitro. OEPs were produced from iPSCs and transplanted into the cochlea of mice. Some transplanted cells moved in the organ of Corti to the site of resident hair cells, developed into hair cell-like cells, and established synaptic connections *in vivo* with the native SGNs.
Betini *et al*., 2018 [28]	Human BM-MSCs ASCs	MSCs were intravenously injected into deafened mice	Mice	Both types of MSCs induced the regeneration of damaged sensory cochlear cells.
Mittal *et al*., 2019 [29]	Rat BM- MSCs	Transtympanic delivery of BM MSCs	Rats	There were ABR and DPOAE, and the cochlear function of the treated animals normalized as compared to the control groups. No inflammatory reactions were detected.
Abd El Raouf *et al*., 2019[30]	Harderian gland-derived stem cells (HG-SCs)	Intravenous injection of HG-SCs	Guinea pigs	In the HG-SC-treated group, both cochlear structure and functions were restored, along with a considerable increase in hair cell numbers, spiral ganglionic cell count, and stria vascularis thickness to levels comparable to those of the control group.
Radeloff *et al*., 2021 [31]	ASCs	ASCs were autologously transplanted into the scala tympani before the insertion of a cochlear implant on one side	Guinea pigs	ASC transplantation enhanced the number of SGNs as well as their peripheral neurites. Mean ABR thresholds were lower, and suprathreshold amplitudes were greater in ASC-transplanted mice, indicating a bigger population of auditory nerve fibers.

Abbreviations: ABR: Auditory brainstem response; ASC: Adipose tissue-derived stem cell; BM-MSC: Bone marrow mesenchymal stem cell; DPOAE: Distortion product otoacoustic emissions; HG-SCs: Harderian gland-derived stem cells; hMSCs: human mesenchymal stem cells; iPSCs: induced pluripotent stem cells; MSC: Mesenchymal stem cell; OEPs: Otic epithelial progenitors; OSC: Olfactory stem cell; SCC: Superior semicircular canal; SGNs: Spiral ganglion neurons.

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Furthermore, the cells must be able to incorporate into the organ of Corti following injection and survive the potentially lethal high potassium concentration of the endolymph [15,16]. Lee et al. evaluated the viability of human embryonic stem cells (ESCs) in the cochlea of deaf guinea pigs preconditioned to have low potassium levels [17]. Their study indicated that temporarily lowering the potassium concentration in the endolymph before transplantation, by flushing it with sodium caprate, contributed to a 1-week survival of human ESCs in the endolymph.

Injecting genes and medications to rejuvenate the present cells of the inner ear is challenging. Researchers have already tested the efficacy of the gene-editing technology CRISPR/Cas9 in treating animal models with autosomal dominant hearing loss [18]. To activate the existing cells, the future treatment will involve combining stem cell therapy, gene therapy, and pharmacological therapy. In 2020, Huang et al. developed an induced pluripotent stem cell (iPSC) line from a 7-year-old male patient with a homozygous *GJB2* c.235delC mutation [19]. Human SOX2, OCT4, KLF4, and c-MYC reprogramming factors were expressed in reprogrammed peripheral blood mononuclear cells. Five iPSC clones were manually selected, grown, and stored; their capacity to differentiate into three germ layers was revealed. Genetic technology can precisely regulate stem cells *in vivo*, ameliorating their applicability in therapies.

4.2. Tympanic membrane (TM)

The TM is a thin membrane between the external and middle ear. TM perforations (TMPs) are a significant issue in otology. While acute TMPs can heal naturally, chronic TMPs require surgery (i.e., tympanoplasty). The standard surgical procedure is performed through tympanoplasty, using the perichondrium or temporalis fascia to rectify the TMP. In regenerative therapy, a range of scaffold materials (e.g., hyaluronic acid [HA], collagen, chitosan, and gel foam), growth factors, and cells have been used as therapies for TMP (Table 3).

4.3. Growth factors in TMP regeneration

Growth factors have been studied for the repair of TMPs. A randomized controlled trial conducted by Lou and Lou included 184 patients with traumatic TMP [32]. The intervention groups received drops containing EGF, FGF-2, and ofloxacin, respectively [32]. The study reported that all treatment groups had significantly shorter closure times than the control group. A randomized controlled trial with 93 study subjects treated with basic fibroblast growth factor (bFGF) displayed a substantially higher closure rate and a considerably shorter closure time in the experimental group than in the control group [33]. Cai *et al.* examined the short- and long-term detrimental effects of fibroblast growth factor-2 (FGF-2) therapy in 134 patients with tympanic perforations. The results revealed that the total closure rate and the closure healing duration were much better in the FGF-2 group [34]. Kanemaru *et al.* investigated the use of fibrin glue and gelatin sponge with bFGF, the use of which demonstrated increased healing rates of complete TMP closure as compared to the control group [35].

4.4. Stem cells in TM regeneration

The use of stem cells in regenerative techniques for TMP recovery has been studied in animal models [36]. Scaffold materials can be used as supporting structures to provide mechanical assistance and deliver cells for cell proliferation and differentiation. Combining scaffolds with MSCs or growth factors has improved TPM healing efficacy. In two studies by Goncalves *et al.*, the combination of BM-MSCs with a HA scaffold or gelatin sponge, respectively, resulted in enhanced TMP recovery [37,38].

In a clinical trial by Vozel *et al.*, [11] patients were given autologous platelet- and extracellular vesicle-rich plasma as a therapy for persistent postoperative inflammation of the temporal bone cavity. A persistent postoperative inflammation of the temporal bone cavity is defined as a chronically discharging radical mastoid cavity that is oftentimes the result of a canal wall-down mastoidectomy. The findings of the trial indicated the remarkable efficacy of autologous platelet- and extracellular vesicle-rich plasma in treating persistent postoperative inflammation of the temporal bone cavity, thereby suggesting its promising use after conventional surgical and conservative therapies have been exhausted [39].

4.5. Ossicles

Through tissue engineering, ossicle reconstruction is performed by cultivating MSCs on bioresorbable 3D scaffolds. Danti *et al.* developed partial ossicular replacement prosthesis (PORP)-like scaffolds with a biocompatible and biodegradable polymer [47]. The poral characteristics were analyzed using micro-CT, and the capacity to support human MSC (hMSC) colonization and osteoblastic development *in vitro* was analyzed quantitatively and qualitatively [48]. The findings demonstrated that the poral characteristics of PORP-shaped scaffolds were necessary to support the colonization of hMSCs and their osteoblastic maturation *in vitro*.

4.6. Cartilaginous craniofacial components

Autologous cartilage is the gold standard for nasal and auricular reconstruction. However, the use of allogenic and synthetic materials for the cartilage is known to increase the risk of tissue rejection, resorption, extrusion, and infection. In this regard, regenerative engineering methods may be preferred as the engineered cartilages closely resemble native cartilages and can be produced in large amounts. In addition, these cartilages can be specifically shaped by harvesting cartilage cells from the auricle or septum and growing them in a specific 3D scaffold. Likewise, growth factors can facilitate the growth and differentiation of the cartilage cells in the scaffold.

In 2004, autologous cultured chondrocytes were utilized in human nose reconstruction for the first time [49]. Yanaga *et al.* extracted the chondrocytes from the conchal cartilage and cultivated them *in vitro*. The chondrocytes were then injected into a subcutaneous pocket above the nasal bone. No complications were reported after a 2-year follow-up period. In 2009, Yanaga *et al.*

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Table 3. Clinical trials of TMP treatment with MSCs, scaffolds, and growth factors

Author	Number of patients/study model	Treatment	Outcome
Raj *et al*., 2011 [40]	42 patients; two groups: 21 patients per group	Tympanoplasty type 1 with acellular dermis was performed in one group, and type 1 tympanoplasty with temporal fascia was performed in the other group (control).	There were no significant differences in terms of the graft success rate and hearing improvement. However, the acellular dermis had a shorter operative time and lesser postoperative pain.
Kanemaru *et al*., 2011 [35]	63 patients; two groups: 53 were assigned to the bFGF group and 10 were assigned to the control group	Fibrin glue and gelatin sponge with bFGF were used in the bFGF group.	There were significantly greater rates of TMP closure in the bFGF group.
Roosli *et al*., 2011 [41]	20 patients; two groups: 10 in the placebo group and 10 in the intervention group	Topical PDGF application on TMPs in the intervention group.	There were no significant differences in terms of success rate (reduction of perforation size by 50% or more) and hearing thresholds between the two groups.
Lou *et al*., 2012 [42]	94 patients; three groups: (1) direct FGF application, (2) FGF via Gelfoam, and (3) control group	Topical FGF, Gelfoam with FGF.	The closure rates in the FGF-treated groups were significantly increased as compared to the control group, but there was no difference in closure rates in patients who received FGF directly and those who received FGF through Gelfoam.
Lou and Wang, 2015 [33]	93 patients; two groups: randomized into control and bFGF-treated groups	Topical bFGF application.	There were significantly higher rates of closure and shorter closure times in the bFGF-treated group than in the control group.
Lou *et al*., 2016 [43]	86 patients; three groups:(1) EGF, (2) bFGF, and (3) control group	Topical bFGF and EGF application.	There was no substantial difference in the closure rates and closure times between the bFGF, EGF, and control groups.
Lou *et al*., 2016 [44]	97 patients; two groups: topical application of EGF in one group and a control group	Topical EGF application.	The total closure rates did not significantly differ between the two groups. The total average closure time in the control group was significantly longer than in the EGF group.
Lou and Lou, 2017 [32]	184 patients; four groups: (1) EGF treatment, (2) FGF-2 treatment, (3) 0.3% ofloxacin drops treatment, and (4) control group	EGF, FGF-2, and ofloxacin drops 0.3% were applied in the three treatment groups, respectively.	The three treatment groups exhibited significantly shorter closure times as compared to the control group. Neither the closure rate nor closure time differed significantly among the three treatment groups.
Zheng Cai *et al*., 2018 [34]	134 patients; two groups: randomly divided into a control group and an FGF-2 treatment group	FGF-2 application on TMP in the treatment group.	The overall closure rate was significantly different between the FGF-2 treatment group and the control group. The FGF treatment group had a considerably shorter closure time than the control group.
Kanemaru *et al*., 2021 [45]	20 patients; non-randomized, single-arm study	A gelatin sponge with bFGF and fibrin glue was applied.	At 16 weeks, complete closure of the TMP was observed in 15 of 20 patients, and the ratio of hearing improvement and air-bone gap was 100%.
Lou *et al*., 2021 [46]	29 patients; two groups: 13 in the bFGF alone group and 16 in the myringoplasty group	bFGF application in one group.	It was indicated that bFGF alone facilitated the repair of chronic and small TMPs but was ineffective for medium-sized TMPs.

Abbreviations: bFGF: basic fibroblast growth factor; EGF: Epidermal growth factor; FGF: Fibroblast growth factor; MSC: Mesenchymal stem cell; PDGF: Platelet-derived growth factor; TM: Tympanic membrane; TMP: Tympanic membrane perforation.

harvested chondrocytes from the auricular cartilage and created a gelatinous chondroid matrix, which was then injected into the nasal dorsa of 75 patients [50]. The gel hardened to form a neo-cartilage within a few weeks, and the cartilages were still functional after 6 years. Autologous nasal septal chondrocytes were used in human exploratory trials in 2014 for nasal alar reconstruction. The cells were cultivated on collagen membranes for 4 weeks before being used for nose restoration in five patients. The patients did not report any complications in the subsequent twelve months and were pleased with the aesthetics and functionality of the reconstructed nose [51]. In 2018, Zhou *et al.* designed a specific scaffold based on a healthy ear for auricular reconstruction in five patients. The scaffold was composed of biodegradable polymers cultivated with autologous chondrocytes. The results were satisfactory, and the

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follow-up lasted for 2.5 years without any incidents of deformation being reported [52]. In 2018, a 7-year-old patient with arrhinia underwent nasal reconstruction using a 3D-printed nasal stent to prevent nasal cavity constriction. In this clinical research, a custom-made silicone nasal stent was manufactured utilizing 3D printing technology. The muco-epithelial tissue successfully regenerated within 2 months following the stent placement. External nose shape, nasal passage structure, and respiratory functions were in good condition after 3 years following the stent removal without additional medical intervention [53].

The most prominent use of auricular cartilage was in 1997 when polyglycolic acid scaffolds were shaped into the 3D structure of a human ear, seeded with bovine chondrocytes, and transplanted into the dorsal pockets of mice [54]. Thereafter, research was carried out in regenerative medicine with synthetic scaffolds and cultured chondrocytes. Yanaga *et al.* injected a combination of autologous serum and autologous chondrocytes from the outer ear cartilage into the ear, nose, and chin of 32 patients with craniofacial or nasal abnormalities [49]. A two-stage transplantation procedure was performed for auricular and nasal/chin reconstructions, respectively [55,56]. In the former, chondrocytes were first extracted from the residual auricular cartilage of four children with microtia and cultivated respectively into a subcutaneous pocket of fascia in the lower abdomen for 4 weeks. Subsequently, the children did not report any adverse events during the 2- to 5-year follow-ups [55]. Similarly, 18 individuals were treated with a comparable nasal/chin reconstructive technique [56].

4.7. Salivary glands

The glands of the upper aerodigestive tract (i.e., parotid, sublingual, and submandibular glands) and minor salivary glands are known to produce saliva [57]. Hypofunctional can be caused by radiation therapy for head and neck cancer, Sjogren's syndrome (SS), and various medications. Possible oral problems caused by hyposalivation include mucosal infections, dysphagia, and aspiration pneumonia. In animal models, BM-MCSs have demonstrated the therapeutic capability to rebuild the salivary glands [58,59]. Xu *et al.* reported a successful restoration of the secretory function of salivary glands in animal models and SS patients using MSC therapy [58]. Adipose tissue-derived stem cells (ASCs) have also been studied in clinical trials on irradiation-induced hypofunctional salivary glands in patients [60]. The phase I/II clinical trial evaluated the efficacy and safety of ASC-based cell therapy, whereby the submandibular glands were injected with autologous ASCs. In the ACS-treated group, the unstimulated total salivary flow rate (assessed after 1 and 4 months) was significantly more than the baseline (pre-treatment). In contrast, the placebo group reported a decrease in salivary flow rate after 1 month and a less prominent increase after 4 months.

5. Applications in Laryngology

5.1. Vocal folds

Lamina propria (LP) is a flexible, collagen- and elastin-rich vibratory connective tissue layer between the epithelium and the muscular tissue of the vocal cords. Trauma, surgery, or long-term vocal misuse are the main causes of scar formation, leading to loss of pliability of the vocal folds. LP scarring causes stiffness and reduces viscosity that changes the tissue biomechanics of the vocal fold [61]. As a result, the normal mucosa wave during phonation is disrupted, thereby affecting the vocals [62,63]. Nonetheless, damaged vocal folds can be regenerated through several methods, including cell therapy, developing and implementing a scaffold, and using growth factors.

5.2. Cell therapy

Fibroblasts and stem cells are extensively studied for vocal fold regeneration. Fibroblasts produce a large proportion of the extracellular matrix (ECM) in the LP and further support the LP. Fibroblasts resemble MSCs because they possess the same cell surface markers and differentiation capacity [63]. Chhetri *et al.* were the first to study the use of autologous fibroblasts from the buccal mucosa. In this study, fibroblasts were injected into the LP of a canine model, subsequently improving the vocal fold mucosal waves and acoustic characteristics. In addition, histological assessments revealed increased fibroblasts, collagen, and reticulin and decreased elastin [64]. Chhetri *et al.* also conducted a pilot study where five individuals with damaged vocal folds were injected with autologous fibroblasts from the buccal mucosa [65]. Four out of five patients demonstrated subjective and objective improvements in the vocal quality and mucosal wave. In another study, Ma *et al.* examined the efficacy of fibroblasts in 15 patients with vocal fold scarring or atrophy using postauricular skin-derived autologous fibroblasts and reported improvements in the mucosal wave without any side effects [66].

Likewise, BM-MSCs have demonstrated positive indications in animal studies [67,68]. In 2020, a phase I/II human clinical trial was conducted with 16 patients to investigate the treatment of vocal fold scarring with autologous BM-MSCs [69]. The patients were followed up for a year, and two-thirds of the participants demonstrated improvements in vocal vibration and flexibility.

There was another phase I/IIA clinical trial that demonstrated the efficacy and safety of adipose-derived regenerative cell-enriched fat grafting to repair glottal gaps following unilateral vocal fold paralysis [70].

5.3. Bioactive factors

Hirano *et al.* studied the use of bFGF in treating atrophic human vocal fold. One week after the bFGF injection, the aerodynamic and acoustic parameters displayed improvements that lasted for 3 months [71]. In a recent study by Hirano *et al.*, local injections of bFGF were performed in 100 cases of vocal fold disease [72]. The findings of the study indicated that intracordal injection of bFGF resulted in voice improvements without any significant adverse effects. Hirano *et al.* also reported that bFGF enhanced the synthesis of HA in fibroblasts and decreased collagen deposition in the vocal folds of aged rats [73]. Subsequently, Hirano *et al.* conducted a clinical trial with 10 patients having aged vocal folds with scar tissue and sulcus vocalis [74]. The findings of the

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trial reported that all patients displayed improvements in speech function and acoustic and aerodynamic measurements.

Hepatocyte growth factor (HGF) is another growth factor that regulates cell proliferation and differentiation and is commonly associated with vocal fold recovery. HGF has an antifibrotic effect and can boost HA levels, reduce collagen production, and stimulate cell growth and migration [75]. In the event of an injury to the vocal folds, HGF can be found in the LP and the epithelium, and its angiogenic and antifibrotic properties could facilitate wound healing of the vocal folds [76]. In one study, it was reported that HGF prevented excessive collagen deposition and restored the levels of elastin, collagen, or HA to normal levels relative to an uninjured vocal fold [77]. Hirano *et al.* also conducted a clinical trial involving 18 individuals with vocal fold scarring or sulcus, and the findings of the trial indicated an improvement in voice measurements [78].

5.4. Vocal fold scaffolds

Several types of scaffolds have been developed for 3D LP replacement, including biological polymers, decellularized organ matrices, synthetic biomimetic hydrogels, and synthetic polymers [79]. These scaffolds can be either injected or attached during surgery, wherein the scaffolds have biomechanical similarities with the LP, transport cells, and other bioactive components. Imaizumi *et al.* successfully employed biodegradable gelatin hydrogel microspheres as a delivery vehicle for bFGF in a rabbit model with vocal fold damage, and the larynxes reportedly displayed better vibratory function and reduced scarring based on histological assessments [80]. HA-modified hydrogel scaffolds have reportedly promoted fibroblast spreading, proliferation, and collagen/glycosaminoglycan production [81]. Likewise, acellular biological scaffolds have similar biological composition and architecture as native tissues. Therefore, the biological scaffolds can facilitate host cell adhesion, motility, and infiltration and secrete pro-angiogenic growth factors [82].

5.5. Larynx

The larynx is composed of multiple tissue types, which presents as a challenge when restoring its function and structure. Patients with an advanced primary tumor have limited treatment options. Total or partial laryngectomy (removal of part or all of the larynx) remains the primary treatment method for advanced primary tumor, but this would lead to speech, breathing, and swallowing deficiencies. Nonetheless, bioengineered laryngeal structures have been developed and tested in animal and human models.

Animal studies have demonstrated that cartilage-like grafts may be effectively employed for partial laryngeal cartilage replacement when stem cells are grown in the scaffolds [48,83]. In contrast, aortic allografts have been utilized to repair hemilaryngeal abnormalities in human studies [84,85]. Brookes *et al.* conducted the first animal study demonstrating that primary skeletal muscle progenitor cells and standardized oligomeric collagen may be used to generate functioning, 3D tissue-engineered skeletal muscle [86].

The human larynx is typically decellularized to effectively produce scaffolds. Baiguera*et al.* evaluated the effectiveness of the modified detergent-enzyme method (DEM) as a decellularization technique for creating human laryngeal acellular matrices that are structurally and mechanically comparable to the original larynx [87]. Twenty-five cycles of DEM created a bioengineered human laryngeal matrix that was physically and mechanically identical to the biological larynx with pro-angiogenic factors. Al-Qurayshi *et al.* evaluated the effect of DEM on the larynx and cricoarytenoid joint of human cadavers. In this study, five fresh frozen human cadaveric larynxes were effectively decellularized, as evidenced by the considerable DNA depletion and ECM preservation, to regenerate a non-immunogenic larynx from a biological scaffold [88]. However, the use of numerous detergents and enzymes in DEM weakened the cricoarytenoid joints. Moser *et al.* recently described the synthesis of laryngeal grafts utilizing decellularized canine laryngeal scaffolds that were recellularized with primary human cells, and this provided the foundation for developing functional laryngeal scaffolds with composite tissue grafts [89]. In another study, Huber *et al.* used a porcine-derived ECM to reconstruct the larynx in mature dogs, demonstrating the constructive remodeling of a xenogeneic acellular biological scaffold material [90]. Thyroid cartilage and thyroarytenoid muscle were restored, and histologic investigation revealed glandular structures, a complete epithelial lining, cartilaginous structures, and skeletal muscle tissue in the reconstructed tissue. The microstructure and macrostructure of the recreated tissue were nearly the same as the original. Porcine laryngeal scaffolds were decellularized and subsequently seeded with human BM-MSCs in two recent studies on laryngeal replacement [91,92]. Both of the studies featured the decellularization of the whole larynx and the production of a safe and biocompatible biological scaffold with the ability to stimulate re-epithelialization and submucosal development. More importantly, the implanted scaffolds supported normal respiratory functions, in addition to proper swallowing and vocalization. The aforementioned studies and their promising results have established the prospect of successful functional partial laryngectomy reconstruction and total laryngeal regeneration.

5.6. Trachea

Patients with congenital malformations or acquired tracheal stenosis after trauma or malignancy are candidates for reconstruction as other minor defects can be easily managed with tracheal resection and end-to-end anastomosis. Airway reconstruction requires a combination of scaffolds seeded with cells. In particular, two studies involving children utilized decellularized deceased donor trachea [2,93,94]. In the first study, the decellularized cadaveric donor tracheal scaffolds were planted with BM-MSCs and autologous epithelium before transplantation in a 12-year-old child suffering from congenital stenosis of the trachea. The child was topically applied with human recombinant erythropoietin to stimulate angiogenesis and transforming growth factor to promote chondrogenesis. At the 2-year follow-up, the child had a functioning airway and had

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returned to school [2]. Subsequently, the 4-year follow-up study reportedly validated the long-term viability of a decellularized tissue-engineered trachea within the child [93]. In the second study, a 15-year-old girl with severe tracheal stenosis was treated with a tissue-engineered decellularized tracheal graft seeded with stem cells [94]. A decellularized tracheal allograft, seeded with autologous respiratory epithelial cells and MSCs, was applied. Early findings were promising, but a critical incident speculated as an intrathoracic hemorrhage, resulted in rapid airway blockage and her subsequent death 3 weeks after the transplantation.

In addition, synthetic scaffolds have been utilized for tracheal restoration. Omori *et al.* were the first to use regenerative procedures to restore the trachea of a thyroid cancer patient [95]. A polypropylene mesh tube coated with a collagen sponge was utilized as a tissue scaffold. The process included right hemithyroidectomy, trachea resection, and scaffold-assisted tracheoplasty. The right side of the three trachea ring segments was removed, and the trachea defect was bridged by suturing the scaffold material. In 2008, Omori *et al.* also utilized similar synthetic implants in four patients to successfully repair their larynx and/or trachea [96].

In animal studies involving aortic allograft, *de novo* regeneration of cartilage was observed within the graft, as well as renewal of ciliated epithelium in the graft lumen [97,98]. This was followed by a clinical trial with six patients [99]. It was reported that the tracheal replacement with aortic allografts was successful in four of the six patients [99]. In a separate study, five patients who underwent trachea reconstruction with human cryopreserved (−80°C) aortic allografts all had favorable outcomes [100]. A similar study reported that thawing cryopreserved aortic allografts enabled viable donor cells to release cytokines and growth factors [101].

Many animal studies have been performed with synthetic 3D-printed scaffolds to determine the materials with the best mechanical properties and also evaluate the effectiveness of graft seeding with autologous cells [102-106]. Kim *et al.* studied the transplantation of a 3D-printed tracheal graft mixed with iPSCs and chondrocytes in a rabbit model [107]. In the study, a tissue-engineered artificial trachea was successfully transplanted into a rabbit model with a 1.5 cm segmental trachea defect. There were no signs of granulation ingrowth in the tracheal lumen, and epithelium and neocartilage successfully formed at the defect sites. According to the research findings by Choi *et al.*, a coating of HA on a hydrophobic tracheal scaffold could improve the adherence of MSCs and tracheal regeneration [108]. In contrast, Pepper *et al.* used synthetic tissue-engineered tracheas in an ovine model. However, it was reported that the transplanted tracheas could not induce optimal epithelialization and neovascularization, and the process led to further complications, such as inflammation and infection [103]. Hence, future studies should focus on scaffold modulation that would accelerate epithelialization and avoid graft devascularization that could lead to graft infection and necrosis.

6. Conclusion

Regenerative medicine is rapidly progressing in the field of otorhinolaryngology and has reportedly restored hearing, voice, and vital functions (e.g., breathing and swallowing) and improved the patient's quality of life. However, the complexity of restoring otorhinolaryngological functions requires further research to refine the techniques used in regenerative medicine.

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Conflict of Interest

The authors declare no conflicts of interest with regard to the content presented in this work.

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ORIGINAL ARTICLE

Comparison between various oral health literacy scales among university students in Jaipur, India

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ABSTRACT

Background: Oral health literacy (OHL) is a multidimensional concept that encompasses reading, writing, speaking, listening, proper decision-making skills, assessment of OHL level, and comparison between scales. Numerous tools are available to measure OHL using a range of indicators.
Aim: The purpose of this study is to compare three OHL scales, namely, Rapid Estimate of Adult Literacy in Medicine and Dentistry-20 (REALMD-20), OHL Adults Questionnaire (OHL-AQ), and Health Literacy in Dentistry (HeLD), among university students in Jaipur, India.
Methods: A comparative study was conducted among 180 university students from non-medical courses. Students' literacy was measured using REALMD-20, OHL-AQ, and HeLD. Independent sample *t*-test, one-way ANOVA, Kruskal–Wallis test, and Pearson's correlation test were used for statistical analysis.
Results: A weak positive correlation coefficient was obtained between REALMD-20, OHL-AQ, and HeLD. The mean REALMD-20 scores of Groups 1, 2, and 3 were 16.3, 14.98, and 15.8, respectively. For OHL-AQ, the mean scores obtained for Groups 1, 2, and 3 were 6.77, 7.50, and 6.58, respectively. The mean HeLD scores in Groups 1, 2, and 3 were 104.23, 102.70, and 100.4, respectively. However, the differences between these groups on all three tested scales were not statistically significant.
Conclusion: In the present study, a weak positive correlation was observed between REALMD-20, OHL-AQ, and HeLD, thereby revealing potential shortcomings in each of these tools.
Relevance for Patients: Encouraging patients to articulate their comprehension of their conditions and instructions enables health-care providers to identify gaps and enhance OHL, leading to effective prevention of oral diseases.

1. Introduction

Oral health is a fundamental component of overall vitality and well-being. Regrettably, dental caries and gingivitis often affect students at an early age, with potential long-term consequences if these oral conditions are neglected [1]. The 20th century witnessed a distinct emphasis on the global importance of health literacy [2], as underscored in a recent report by the World Health Organization (WHO), which highlights the pivotal role of health literacy as a primary determinant of health-care outcomes. According to WHO, health literacy encompasses socio-cognitive skills influencing an individual's motivation, capacity, and proficiency in acquiring, comprehending, and applying information essential for advancing healthcare [3].

Health literacy, a multi-dimensional concept, extends to knowledge about oral diseases in dentistry and is influenced by an individual's literacy proficiency, psychosocial interactions,

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and diverse health situations [4]. Oral health literacy (OHL) represents a comprehensive concept, encapsulating proficiencies in reading, writing, numeracy, effective communication, attentive listening, and sound decision-making skills [5]. Globally, the surge in interest surrounding OHL is fueled by disparities in oral health, particularly among vulnerable populations where conditions such as dental caries and periodontal disease substantially contribute to the global disease burden [6-10].

To assess an individual's health literacy, various tools have been developed, with a significant focus on the overall health commonly utilized in research investigations. The Health Literacy in Dentistry (HeLD) tool has emerged as a reliable, valid, and culturally acceptable instrument specifically designed to assess OHL among vulnerable populations. HeLD has demonstrated discriminative capabilities, revealing significant differences in three oral health perception factors—self-rated general health, self-rated oral health, and oral health impact [11]. In addition, the OHL-Adult Questionnaire (OHL-AQ) serves as a dependable tool for evaluating the functional aspect of adults' OHL within communities or populations [5].

The OHL-AQ, a pioneering instrument, assesses two crucial OHL-related skills—"listening" and "decision-making." It stands out for its brevity and ease of use and is applicable in both clinical and research settings to enhance oral health-related literacy skills and dentist-patient communication. Another noteworthy tool, REALMD-20, a concise screener for dental and medical health literacy, consists of 20 items featuring satisfactory psychometric characteristics [12]. The validity of this tool has been confirmed by correlating it with the Rapid Estimate of Adult Literacy in Medicine (REALM) [13] and the Test of Functional Health Literacy in Adults (TOFHLA) [14], which are widely accepted instruments for assessing medical health literacy.

As poor OHL emerges as a new public health challenge, the imperative for a dependable, valid, and culturally appropriate tool for its evaluation becomes evident. Within the past decade, advancements in defining health literacy have spurred the development of a diverse range of measurement instruments, encompassing a broad spectrum of abilities from reading comprehension to numerical proficiency. Notably, a study in Rajasthan revealed low OHL among children and teenagers, emphasizing the need for comprehensive interventions [15].

The rationale for the present research stems from the recognition that the university student population comprises individuals from diverse rural and urban backgrounds. By investigating their OHL, we aim to garner insights into their comprehensive oral health-related knowledge, acknowledging potential variations between students. The outcomes of this study will not only contribute to a better understanding of oral health needs specific to university students but will also facilitate comparisons between different scales used to measure OHL. Furthermore, these findings could inform educational interventions and public health strategies to promote better oral health outcomes among students from diverse regions. At present, there is a dearth of studies comparing different OHL scales, making this study pivotal in addressing this gap. The primary objective of this study is to compare OHL outcomes from different scales in a selected population of university students in Jaipur, India.

2. Methods

This comparative study aimed to assess and compare the OHL levels of university students using three different scales: OHL-AQ, REALMD-20, and HeLD scales. This study was conducted in the Department of Public Health Dentistry at NIMS Dental College in Jaipur, India. The study involved 180 students from NIMS University, who were divided into three groups based on their course of study. Students who were 18 years or older and able to communicate in English were recruited and included in this study, while medical and paramedical students and those with incomplete questionnaires were excluded from the study. Ethical clearance was obtained before the study from the Institutional Ethics Committee of NIMS Medical College (protocol no.: NIMSUNI/IEC/2017/14). Written informed consent was obtained from all participants.

A pilot study was conducted with 10% of the population to test the feasibility of the study. The study pro forma was administered to 180 students, who had been divided into three groups: Group 1 (commerce, science, and humanity courses), Group 2 (engineering and architecture courses), and Group 3 (management courses). Sociodemographic information, such as name, age, sex, and course of study, was collected from each participant.

Three scales were used to measure students' OHL: OHL-AQ, REALMD-20, and HeLD. OHL-AQ is a 17-item questionnaire that assesses adults' OHL in community-based studies. The questionnaire had four sections: reading comprehension, numeracy, listening, and decision-making. Scores were divided into three categories: inadequate (0–9), marginal (10–11), and adequate (12–17).

REALMD-20 is a 20-item reading recognition test that screens basic dental health literacy and reading ability. The interviewer asked participants to read each word aloud. Scores were divided into three categories: inadequate (0–11), marginal (12–13), and adequate (14–20).

HeLD is a 29-item questionnaire that assesses OHL based on the constructs identified in the HeLMS. The questionnaire has seven domains: receptivity, understanding support, economic barriers, access, communication, and utilization. Scores were divided into three categories: inadequate (0–61), marginal (62–77), and adequate (78–116).

The completed questionnaires were collected and the data were entered into Microsoft Excel worksheets. The collected data were analyzed using IBM SPSS software for Windows, version 20 (IBM Corp., Armonk, N.Y., USA), and the results are expressed as means, standard deviations, and descriptive statistics. Independent sample *t*-tests and one-way ANOVA were performed to compare OHL levels between groups and between categories of scores on the literacy scales. Pearson's correlation coefficient was used to correlate the scores from the different literacy scales. Normality of the data was tested using the Shapiro–Wilk test. Data were normally distributed.

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3. Results

In this study, there were a total of 180 participants, with 112 (62.22%) being male and 68 (37.78%) being female. The mean scores for HeLD in different domains, including receptivity, understanding, support, economic barriers, access, communication, and utilization [3], were 17.75, 10.55, 10.572, 10.439, 13.961, 24.89, and 14.27, respectively.

Independent sample *t*-tests were conducted to compare the mean OHLAQ, HeLD, and REALMD-20 scores based on gender. The results showed a statistically significant difference in mean OHL-AQ scores between males and females. However, the mean difference in HeLD scores between males and females was not statistically significant, with males scoring 101.16 and females scoring 104.56. The mean REALMD-20 score for males was 15.08, while for females, it was 16.74, and the difference between these scores was statistically significant (Table 1).

The study also compared the categories of scores (adequate, marginal, and inadequate) obtained using the different study tools. The results revealed a statistically significant difference between these categories. However, when comparing the mean OHL scores among the study groups using one-way ANOVA, the differences were not statistically significant (Table 2).

Finally, the study investigated the correlation between OHL-AQ and HeLD, HeLD and REALMD-20, and REALMD-20 and OHL-AQ using Pearson's correlation coefficient. The results showed a weak positive correlation (Pearson's correlation coefficient = 0.155) between these variables (Table 3).

Table 1. Comparison of the mean OHL-AQ, HeLD, and REALMD-20 scores based on gender

Scales	*N*	Mean	SD	SEM	*t*-value	*P*-value
OHL-AQ						
Male	112	6.2	3.626	0.343	−3.548	0
Female	68	8.19	3.707	0.449		
HeLD						
Male	112	101.16	16.741	1.582	−1.5	0.135
Female	68	104.56	10.606	1.286		
REALMD-20						
Male	112	15.08	3.799	0.359	−3.213	0.002
Female	68	16.74	2.429	0.295		

Abbreviations: SD: Standard deviation; SEM: Standard error of the mean.

Table 2. Comparison of mean oral health literacy score among the study groups using one-way ANOVA

Scales	Group	*N*	Mean	SD	SE	*F*-value	*P*-value
OHL-AQ	1	60	6.77	3.788	0.489	0.991	0.373
	2	60	7.5	4.065	0.525		
	3	60	6.58	3.441	0.444		
HeLD	1	60	104.23	11.198	1.446	1.022	0.362
	2	60	102.7	15.084	1.947		
	3	60	100.4	17.401	2.246		
REALMD-20	1	60	16.3	2.316	0.299	2.298	0.103
	2	60	14.98	4.597	0.594		
	3	60	15.8	2.9	0.374		

Note: Group 1 comprises students pursuing commerce, science, and humanity courses; Group 2 comprises students pursuing engineering and architecture courses; Group 3 comprises students pursuing management courses. Abbreviations: SD: Standard deviation; SE: Standard error.

Table 3. Correlation between REALMD-20 and OHL-AQ using Pearson's correlation coefficient

Correlation	Mean	SD	*N*	Pearson's correlation coefficient	*P*-value
OHL-AQ and HeLD					
OHL-AQ	6.95	3.773	180	0.155	0.038
HeLD	102.44	14.786	180		
HeLD and REALMD-20					
HeLD	102.44	14.786	180	0.164	0.028
REALMD-20	15.71	3.436	180		
REALMD-20 and OHL-AQ					
REALMD-20	15.71	3.436	180	0.244	0.001
OHL-AQ	6.95	3.773	180		

Abbreviation: SD: Standard deviation.

4. Discussion

Adolescence represents a unique phase of human growth, characterized by not only physical but also emotional and cognitive changes. At the age of 18, these young individuals stand at the threshold of a new chapter in their lives, as society recognizes them as legal adults. This study recruited participants from colleges with diverse student backgrounds to capture the current state of OHL among undergraduate students. The students were recruited from various constituent colleges of NIMS University, Jaipur. The sampling approach was chosen to accommodate the study's requirement of having participants complete three questionnaires. Although English was not the primary language spoken in the participants' homes, the study was conducted in English because much of the health information in health-care settings is available in this language. The study tool was validated in English and not in the local language (Hindi).

In our study, we observed that the mean OHL-AQ scores for males and females differed, with females scoring higher in OHL. This finding contrasts with a study by Chowdhary *et al*. (2016) [16] in South India and Naghibi Sistani *et al.* (2014) [5] who found no gender difference in OHL. This discrepancy could be attributed to the fact that our study participants belonged to a younger age group. Similarly, Basir *et al*. [17] found that OHL scores were higher among females.

This study demonstrated a statistically significant difference between the score categories. In research conducted by Charophasrat *et al*. [18], they discovered a relatively high OHL score of 73.4% of participants demonstrating adequate OHL. This percentage was notably higher than that reported by Schaeffer *et al*. [19]. Conversely, a study conducted in Germany revealed that only 14.9% had excellent health literacy, 39.3% had sufficient health literacy, 33.7% had problematic health literacy, and 12.1% had inadequate health literacy [20]. Basir *et al.* [17] conducted a

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cross-sectional study on 254 middle school students and reported that OHL level of 50.2% of the students was inadequate.

We also identified a weak positive correlation between OHL-AQ and HeLD, HeLD and REALMD-20, and between REALMD-20 and OHL-AQ, highlighting the distinct constructs measured by these instruments. Similar results were obtained in a study conducted by Devi [21] in 2011 in Bangalore city. The low correlation between the tested instruments can be attributed to the fact that these three instruments possess distinct constructs and measure different facets of OHL. REALMD-20 is a word-recognition test [12], OHL-AQ evaluates listening and decision-making skills [5], whereas HeLD accounts for the multidimensionality of OHL by encompassing the domains of communication, access, receptivity, understanding, utilization, support, and economic value [11].

In various research studies, a diverse set of assessment tools have been employed to gauge individuals' OHL. For instance, in one study, researchers utilized the REALMD-20 word-recognition tool along with the Comprehensive Measure of Oral Health Knowledge to assess conceptual knowledge [22] and also incorporated the Hong Kong OHL Assessment Task for pediatric dentistry as well as the Russian version of the OHL Instrument in separate investigations [23,24]. These instruments were chosen to evaluate reading comprehension and numeracy skills. It is important to note that all these assessment tools determine OHL by aggregating scores, where higher scores indicate a higher level of OHL.

However, contrasting results were obtained by Gong *et al.* [14], where they achieved strong evidence of a correlation between Test of Functional Health Literacy in Dentistry (TOFHLiD) and Rapid Estimate of Adult Literacy in Dentistry-99 (REALD-99). This may be due to the difference in the scales used to measure OHL. The reason for a strong correlation between TOFHLiD and REALD-99 may be due to the fact that both scales were derived from TOFHLA.

Using REALD instruments, we only tested a person's reading ability and could not capture comprehension, as reading is considered intermediate to decoding and comprehension [5]. This assessment tool lacks the capability to gauge word comprehension, posing challenges in discerning whether individuals who indicate English is not their primary language might be mispronouncing words they are familiar with and comprehend. It is known that there is a correlation between race, education, and considering English as a secondary language. One strategy involves emphasizing linguistically and culturally suitable communication methods during all interactions between patients and providers. This approach can be beneficial for individuals whose main language is not English and who face challenges not necessarily related to their knowledge of health terminology, but rather with pronunciation. Additional research is needed to examine the full array of literacy skills, including reading, writing, speaking, and listening [4]. This study encompassed undergraduate students from diverse academic backgrounds, excluding those in the health sciences. To gain a comprehensive understanding, future research is needed to explore a sample representative of all segments of society [5].

Despite recent research advances in the field of health literacy, specifically in the context of OHL, a notable gap remains in understanding the primary causes of poor oral health-related literacy skills, particularly in developing countries. Factors such as the scarcity of accessible oral health information resources, the presence of complex oral health instructions and brochures, and the lack of preparedness among dentists to assess patients' literacy needs have not yet been widely recognized. In Iran, for instance, a significant portion of oral health information materials, including medication labels, postdental treatment instructions, and oral health guidance, are provided in a foreign language, typically English. This linguistic barrier can pose considerable challenges for patients attempting to comprehend the information provided to them. Furthermore, dentists often utilize specialized dental jargon and numerous English terms, further complicating communication between dentists and patients [25]. Individuals with exceptionally low scores on health literacy assessments may encounter significant obstacles in their interactions with oral health providers. Thus, it is imperative to dedicate special efforts to developing culturally sensitive assessment tools tailored to the evaluation of OHL [7].

Naghibi Sistani *et al*. introduced and conducted a pilot test of the OHL Adults Questionnaire (OHL-AQ) to establish its validity and reliability [5]. The OHL-AQ comprises four sections: reading comprehension, numeracy, listening, and decision-making. This novel instrument was designed to overcome the shortcomings of current OHL assessments, which are often lengthy, lack applicability to diverse populations, and primarily focus on specific dental health terminologies or understanding oral health information and numerical calculations [26,27]. The authors concluded that the inclusion of two new measures (listening and decision-making) enhances the overall effectiveness and quality of existing instruments. They suggest that future research should involve a more extensive and diverse population, with a particular focus on exploring the factors influencing OHL, especially among individuals with limited general literacy skills [28,29].

Jones *et al*. [11] introduced the HeLD, building on the Health Literacy Measurement Scale (HeLMS) [13]. The theoretical constructs integrated into HeLD emphasize the significance of a person's ability to seek, comprehend, and apply oral health information, which is crucial for accessing and benefiting from oral health-care services. The researchers highlighted that studies utilizing HeLD can be of interest to both those working with marginalized and mainstream groups on OHL measurement. The authors envision several potential applications for this instrument. First, public dental services could employ it in health service evaluations to assess potential barriers to service delivery and service uptake, aiming to enhance attendance for oral care and potentially improve oral health impacts within communities. In addition, oral and allied health practitioners might use HeLD to conduct oral health needs assessments, both for communities and potentially for individuals they serve. Finally, HeLD could find applications in research studies aimed at exploring the factors influencing oral health and developing brief explanatory concepts for oral health outcomes. Charophasrat *et al*. [18] conducted

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a study that revealed that individuals with an adequate level of literacy possess both proficient reading and critical thinking abilities, enabling them to apply information effectively to enhance their oral health. In addition, the study found that over 50% of the participants incorporated daily practices, such as flossing and using mouthwashes. These individuals demonstrate the ability to effectively apply their knowledge in various contexts, whether in their homes and communities while shopping in the marketplace, accessing oral health services, or recognizing their rights to access different services. Due to their enhanced OHL, it is not surprising that this particular group exhibits more favorable behaviors, such as regular use of oral hygiene tools like floss and mouthwash, as well as a higher frequency of dental check-ups in the past 6 months compared to individuals with limited OHL. These findings align with the health promotion model proposed by Nutbeam [30] and the health literacy model developed by Sørensen *et al*. [31].

Jones *et al*. [23] discovered that individuals with insufficient OHL tend to make fewer visits to dentists and have poor oral health. In addition, Baskaradoss *et al*. [32] revealed a connection between the OHL of caregivers and the dental status of children, as reflected in their DMFT/dmft scores.

According to Fazli *et al.* [33], demographic and socioeconomic factors are differentially correlated with oral health behaviors and oral health status. In contrast to our study, all students were of the same age and background; therefore, sociodemographic factors did not play a major role in the study.

The study was constrained by its relatively small sample size. Enrolling students from a wider range of courses can strengthen their validity. The presence of language barriers posed challenges during the research. It is important to note that this study focused on a specific area and did not include an assessment of sociodemographic factors.

In this study, we recommend that, due to low OHL, professionals or doctors should use local terminology when communicating with patients and limit the use of medical jargon. Doctors need to make extra efforts to ensure that patients understand the instructions given by doctors. Therefore, oral health awareness programs should be conducted to improve health literacy. Although the participants conversed in English with the examiner, their English fluency was not assessed. Hence, tools to assess literacy and English fluency should be incorporated in future research. Health professionals can identify knowledge gaps, comprehension difficulties, and misinterpretations by asking patients to explain their understanding of their condition and instructions. OHL contributes significantly to oral health, and improving it can prevent numerous oral diseases. Building navigable and accessible care systems is crucial for enhancing the health of the population. Efforts to enhance OHL and primary/secondary prevention are interconnected, leading to optimal oral health and early detection and treatment of oral diseases. Understanding oral health issues and the role of OHL will enable better care and education for at-risk populations. However, there are limited tests specifically designed to assess OHL.

5. Conclusion

This study categorized the scores into adequate, marginal, and inadequate levels. Adequate OHL is correlated with better oral health behaviors among students. Current tools tend to focus heavily on word-recognition, numeracy, and reading skills, and lack emphasis on health behaviors and service utilization. Specific population-adapted tools, ensuring acceptability and cultural competence, are necessary. In addition, tools should assess risk and effectively measure intervention-induced changes. The key practical challenge in assessing OHL in study groups revolves around the validation of assessment tools in the local language. Providing accessible information to those with inadequate literacy can promote behavioral changes and improve oral health outcomes. Oral health promotion programs should provide information at a comprehensible level for inadequately literate people, to foster behavioral changes and better oral health outcomes.

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Conflict of Interest

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participant

Ethical clearance was obtained before the study from the Institutional Ethics Committee of NIMS Medical College (reference no.: NIMSUNI/IEC/2017/14) and written informed consent was obtained from all participants.

Consent for Publication

Not applicable.

Availability of Data

Data can be obtained from the corresponding author on request.

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REVIEW ARTICLE

Identification of the essential and critical factors of decision-making for COVID-19 patient management: a mixed-method study

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Abstract

Background: Understanding the contributing factors for decision-making based on the disease stage is highly crucial to improving patient care.
Aim: This study aimed to identify the critical and essential factors to enhance clinical decision-making for COVID-19 patients.
Methods: This mixed-method research was conducted in two phases. In the first phase, a systematic literature review was performed using defined search strategies across four databases, including PubMed, Scopus, Web of Science, and IEEE. A total of 136 studies were obtained. Next, a questionnaire-based survey was conducted to validate the findings from the review and to categorize the factors into essential and critical factors. The content validity ratio was used to categorize the factors accordingly. The identified factors were classified into six main categories based on the stages of care and the corresponding decision-making.
Results: The expert panel consisted of 10 clinicians from various fields. The potential factors were categorized into six categories. A total of 293 factors were found in the literature review. The findings of the consensus survey revealed 10 factors related to the decisions on the length of stay, eight factors for ward referral decisions, one factor for decisions on home referrals, six factors for deterioration diagnosis decisions, two factors for discharge decisions, and 10 factors for decisions on intensive care unit referrals. In addition, the study identified respiratory rate, oxygen saturation at administration, arterial oxygen pressure, sequential organ failure assessment score, and glomerular filtration rate as significant decision-making factors for COVID-19 patient management.
Conclusion: For medical emergencies (e.g., COVID-19 management), fewer but more significant factors may increase the efficiency of decision-making, thereby improving the quality of patient management. On this basis, this study identified the essential and critical factors for decision-making at different stages of COVID-19 patient management.
Relevance for Patients: This study identified the most important factors in diagnosing the deterioration of COVID-19 patients to improve the treatment outcome of COVID-19 patients.

1. Introduction

The COVID-19 pandemic has been known as a global challenge that requires inclusive approaches to control. COVID-19 is caused by a new virus that was officially named

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severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Most people infected with this virus experienced mild to moderate respiratory diseases. Besides epidemiological policies, patient-centric decision-making has been highly crucial to control the COVID-19 pandemic. Particularly, at the pandemic peak, physicians had to make crucial decisions, based on widely recognized factors, for patient management within a short time [3,4].

However, COVID-19 management is highly inconsistent due to symptom variations, ranging from mild to severe symptoms [5,6]. Therefore, the management of COVID-19 patients is a multi-criteria decision-making problem due to the complexities of COVID-19 [7]. There are different decisions to be made for each patient based on their condition [8]. These decisions could include referrals to the intensive care unit (ICU) or isolation at home. A COVID-19 patient may be assigned to a specific stage, typically inclusive of discharge, ambulatory, inpatients, referral to the ICU, or death due to COVID-19 infection [9]. In these circumstances, identifying the necessary factors can be significantly effective in making the best decision.

Nonetheless, information is the key element for decision-making, and decisions are made based on the most influential factors. Likewise, more data may not result in the best decision being made, but the most effective data provides the best care and safety for patients. Hence, we aim to identify the most fundamental factors for the best decision-making in COVID-19. In times of emergency, decision-making is critical, and the most influential factors result in the best decision-making [10]. In such situations, heuristic decision-making is adopted, whereby humans process information in a less complex way to reach better decisions more efficiently. The heuristic approach can be more accurate for complex problems and is one of the most important discoveries of recent decades [11]. This type of decision-making is suitable for COVID-19 as heuristics account for the uncertainty and risky conditions of COVID-19. Therefore, it is essential to prioritize the effective factors, especially during an influx of patients. The priority of the factors should account for the patient's condition and the presently available evidence to ensure that clinical experts can make optimal, timely, and accurate decisions [12]. While previous studies have determined the general factors affecting the status of COVID-19 patients [13-16], our study further identified the critical and essential factors for optimal decision-making and rapid management of COVID-19 cases based on disease severity. Recent studies have revealed that different approaches were considered to manage and prioritize infected patients, varying from home isolation to ICU admission [17,18]. Thus, the effective factors regarding clinical decision-making and different approaches to managing admitted patients can be divided into six categories, comprised of (i) effective factors related to the length of stay, (ii) effective factors related to ward referrals, (iii) effective factors related to home referrals or home isolation, (iv) effective factors related to deterioration diagnosis, (v) effective factors related to identifying the discharge time, and (vi) effective factors related to ICU referrals [19-25]. Thus, the main objective of our study was to determine the essential and critical factors for decision-making based on case severity and disease stage through a systematic review and the opinions of clinicians.

2. Methods

This mixed-method study was conducted in two main phases, including a systematic review and a questionnaire-based survey for a panel of clinical experts. We employed a combination of quantitative and qualitative analyses within the same study, enabling the exploration of diverse perspectives and relationships that exist between the complex layers of our multifaceted research questions [26].

2.1. Research question

This study was based on the following research question: What are the critical and essential factors for optimal decision-making and rapid management of COVID-19 cases based on disease severity?

2.2. Systematic literature review

2.2.1. Search strategy

Articles from PubMed, Scopus, Web of Science, and IEEE databases were searched from December 2019 to December 2022. The searched keywords included "triage," "classification," "scoring system," "forecasting," "predict," "prediction," "ICU," "critical care unit," "severe acute respiratory syndrome coronavirus," "COVID-19," "SARS-CoV-2," "2019 novel coronavirus," "Wuhan coronavirus," and "novel coronavirus." The patient/population, intervention, comparison, and outcomes model was used to define the search strategy [27]. This search was restricted to English language papers. The search strategy is provided in Table A1.

2.2.2. Inclusion criteria

The inclusion criteria were articles published in English and focused on decision-making regarding COVID-19.

2.2.3. Selection process

Conference abstracts, letters to editors, papers with unavailable full text, and papers with insufficient details about the data elements (i.e., factors) were excluded from this review. This systematic review was conducted based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist [28].

2.2.4. Data extraction

After duplicate articles were removed, the article citations were imported to EndNote. In the first phase, all titles and abstracts of the articles were independently examined by four authors based on our main objective to select relevant studies. Another author reviewed a sample of studies at random to validate the process. Next, all of the articles were categorized into six main categories, i.e., decision-making for patient ward referrals, patient ICU referrals at the golden time, length of stay in the inward and/or the ICU, patient deterioration diagnosis, and patient discharge. These categories

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of possible outcomes for each patient were defined based on the clinicians' views and agreement. The six potential areas of decision-making were considered through expert consultation to classify the influential factors extracted from the reviewed publications. The flow of the literature review process is displayed in Figure 1.

2.2.5. Identifying potential factors and questionnaire preparation

To determine the essential and critical factors of decision-making for COVID-19 patients based on the severity, a datasheet/form (prepared based on the PRISMA checklist) was used to identify data elements (i.e., factors) in the articles of the systematic review. This datasheet included four sections; name of the data element, *P*-value, category, and description.

The full-text eligible studies were assessed thoroughly by four reviewers to extract potential datasets related to each category. If the *P*-value was reportedly <0.05, the factor was considered as a potential data element. If there was a disagreement between the authors in the selection of relevant studies, the final decision was made by another author (i.e., S.R.N.K.).

Thereafter, a five-point Likert-based questionnaire was created based on the potential factors identified through the literature review. The questionnaire was finalized with reference to the factors identified from the systematic review and the six outcomes. The questionnaire consisted of two parts; the demographic characteristics of experts and a list of factors that was scaled according to the Likert score.

2.3. Expert consensus and questionnaire-based survey

Expert consensus refers to the collective opinions of clinical experts on a clinical topic and it is employed to provide quantitative and reliable data (e.g., recommendations of best practices) in clinical areas that are not well-defined by research [29,30].

2.3.1. Validating the contents of the questionnaire

The clinical experts who participated in the survey were affiliated with various medical universities, clinics, and hospitals in Iran. The selected participants in this study comprised specialized physicians in internal medicine, pulmonary and infectious disease, emergency medicine, and related clinical fields with experience in COVID-19 patient management for more than 6 months.

Five clinical experts were invited to assess the grammar, language, and item allocations for validating the questionnaire. The experts were requested to suggest a correction for items that they deemed were incorrect. Each question (data element) was to be evaluated by the participants over a five-point scale, ranging from "essential" (score: 1) to "highly critical" (score: 5).

2.3.2. Recruitment of experts for consensus-based survey

Some criteria referred to specific clinical experts, warranting their invitation to the study. These clinical experts had experience working in COVID-19 wards or ICUs in multiple hospitals in Iran. In addition, a general practitioner with relevant experience

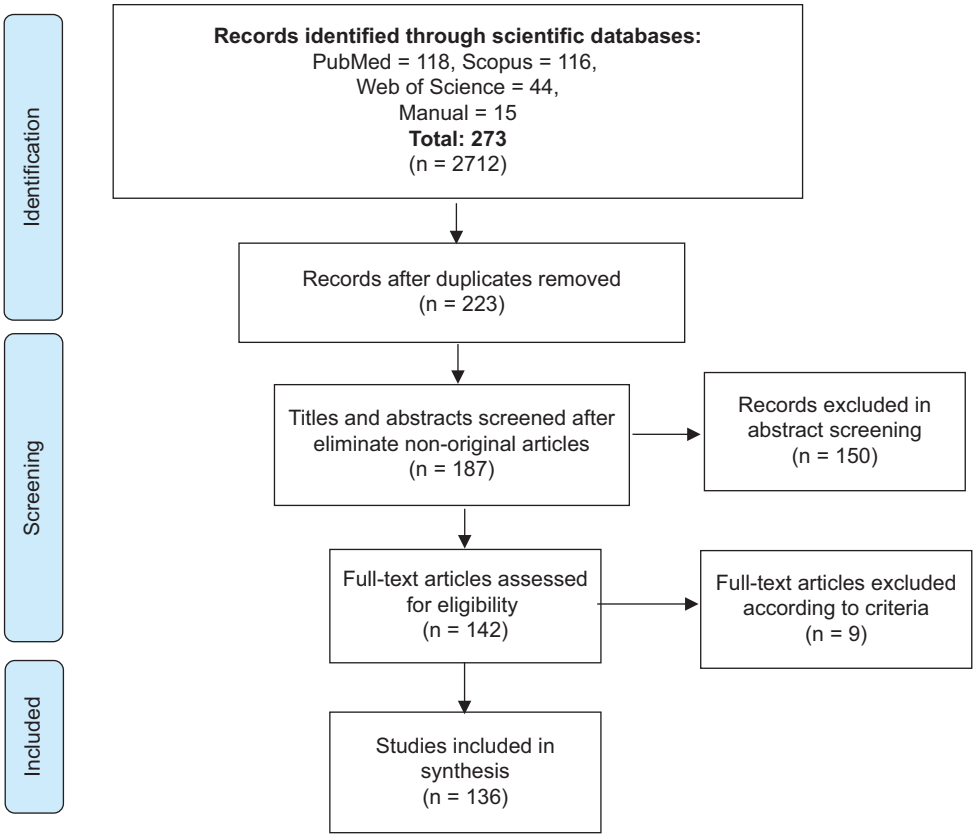

Figure 1. The flow of the literature review process.

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and interest in the study would be invited to participate in the study as well. With reference to the Lawshe table [31], the number of participants was limited to 10 clinical experts for an optimal content validity ratio (CVR) during expert agreement analysis.

2.3.3. Conducting the questionnaire-based survey

We conducted the questionnaire-based survey by initially sharing an online link to the questionnaire with the clinical experts through email or social network. The objective of the survey was explained to the clinical experts through the same email or content of the message (if the experts were contacted via social network). The clinical experts would confirm their participation with a declaration. CVR [31] was utilized to quantitatively evaluate content validity, and the content validity index (CVI) was calculated for each data element. The CVR corresponded to the essentiality or effectiveness of each item in clinical decision-making for COVID-19 patients.

The critical threshold of CVR refers to the minimum CVR critical value for each item. Based on Lawshe's table [32], the critical threshold of CVR was set at 0.62 per the number of clinical experts (i.e., 10 clinical experts in this case).

2.3.4. Analysis of panel results

The literature review generated a list of factors that could effectively decide a patient's outcome. Herein, we added several criteria when interpreting the results. If the CVR of an item was greater or equal to the CVR threshold, the item was considered "critical." Items with CVR between zero to the threshold value (i.e., 0.62) were considered "essential," implying an agreement from more than half of the clinical experts on the particular item. A sub-zero CVR would indicate that less than half of the clinical experts considered an item "essential," and the item would subsequently be rejected [33,34]. All of the results were analyzed using IBM statistical package for the social sciences v20.

3. Results

This study was conducted in various steps, and the results of each step, with the identified factors and their frequency, are represented in Figure 2.

The possible outcomes identified from the literature review in the first step were divided into six possible categories (as follows):

(i) Length of stay: The length of stay is a clinical metric that measures the time elapsed between a patient's hospital admittance and discharge [35].
(ii) Ward referrals: Ward referrals involve directing a patient to a different hospital ward based on their specific medical condition.
(iii) Home referrals: Home referrals involve recommending and arranging for patients to receive care in the comfort of their own homes instead of being admitted to a medical facility.
(iv) Deterioration diagnosis: Deterioration diagnosis indicates the worsening of a patient's health condition which can happen at any point while they are hospitalized.
(v) Discharge: Discharge is when a patient is permitted to leave the hospital following the receipt of treatment and care.
(vi) ICU referrals: ICU referrals entail recognizing patients in need of specialized care and moving them to the ICU for treatment.

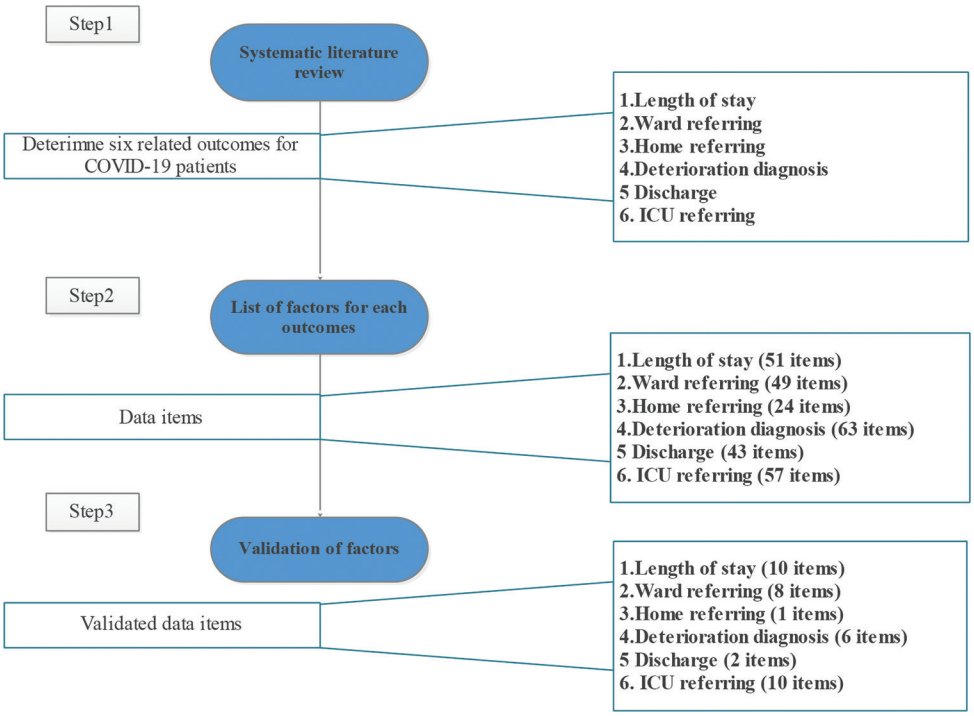

Figure 2. The study process included a systematic review and the validation analysis of factors affecting the physicians' decision-making for COVID-19 patients.

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In the second step, the factors were validated concerning each outcome via CVI calculation, and the critical factors were determined.

3.1. Literature review to identify the effective factors

Overall, 273 articles were obtained from the literature search. Fifty duplicate studies were removed accordingly. After assessing the title, abstract, and full text of the articles and excluding the irrelevant studies, the remaining 136 articles were further evaluated. The articles were evaluated for the relevant factors (e.g., effective factors and clinical tests in COVID-19 management) based on predefined categories regarding decision-making. The general characteristics of the evaluated articles are displayed in Table 1.

From the literature review, a total of 293 demographic and clinical factors, considered effective in clinical decision-making at different stages of COVID-19, were identified. Among them, 51 factors were related to the length of stay, 50 factors were related to ward referrals, 24 factors were related to home referrals, 63 factors were related to deterioration diagnosis, 43 factors were related to discharge, and 62 factors were related to ICU referrals. It should also be noted that several factors are common in various areas.

3.2. Clinical expert panel data analysis

The clinical expert panel included one subspecialist, six specialists, and three general practitioners with experience working in COVID-19 wards or ICUs in referral academic hospitals in Iran. Six of the participants worked in Tehran, while the others worked in Kerman, Varamin, Yasuj, and Dehdasht. Table 2 summarizes the characteristics of these clinical experts based on gender, medical specialty, clinical experience, and the number of COVID-19 patients visited from March 2020 to December 2022.

3.3. Essential and critical factors

Based on the calculated CVRs of 258 items, 159 items were identified as essential factors, and 28 items were identified as critical factors in the six outcome categories. A total of 71 items were rejected based on our criteria described in Section 2.3.5. The full results are displayed in Tables A2-A7.

The first category of factors was associated with decision-making regarding the length of stay in the hospital (Table A2). From a total of 51 factors, 10 were considered critical and 41 were considered essential. The critical factors were the history of cancer or malignancy, history of any cardiovascular disease, history of renal function impairment or chronic kidney disease, history of respiratory disease (e.g., asthma and chronic obstructive pulmonary diseases [COPD]), history of using immunosuppressive drugs, respiratory rate (RR), C-reactive protein, glomerular filtration rate (GFR), oxygen saturation (SpO_2) at admission, and the sequential organ failure assessment score.

The second category (i.e., ward referrals) included 49 factors (Table A3), of which eight factors were considered critical. The accepted factors were the history of diabetes mellitus, history of cancer or malignancy, history of any cardiovascular disease, history of renal function impairment or chronic kidney disease, history of respiratory diseases (e.g., asthma and COPD), RR, SpO_2 at admission, and arterial oxygen pressure (PaO_2). A total of 24 factors were reported for home referrals or home isolation, of which one factor (i.e., SpO_2) was considered critical, while the other 23 factors were deemed essential (Table A4).

The fourth category of decision-making was related to the factors in deterioration diagnosis (Table A5). This category reported 63 factors, including six critical factors and 57 essential factors. The critical factors for this decision-making were the history of respiratory disease (e.g., asthma, COPD, and other similar diseases), RR, D-dimers, SpO_2 at admission, venous blood pH, and PaO_2.

The discharge category (with a total of 43 factors) reported two critical elements, including RR and GFR (Table A6).

The sixth category was ICU referrals with 57 factors in total (Table A7). Among them, there were 47 essential factors and 10 critical factors. The critical factors were body mass index or obesity, history of cancer or malignancy, history of renal function impairment or chronic kidney disease, history of respiratory disease (e.g., asthma, COPD, and other similar diseases), RR,

Table 1. General characteristics (i.e., type of clinical decision and country) of the evaluated articles

Characteristic	Number of articles (relative to all articles [%])
Type of clinical decision	
Length of stay	12 (8.89)
Ward referrals	9 (6.67)
Home referrals	4 (2.96)
Deterioration	98 (72.59)
Discharge	15 (11.11)
ICU referrals	30 (22.22)
Country	
China	53 (39.26)
United States of America	22 (16.30)
Italy	17 (12.59)
France	9 (6.67)
Turkey	6 (4.44)
Iran	4 (2.96)
Belgium	2 (1.48)
Canada	3 (1.48)
Germany	4 (1.48)
Greece	5 (1.48)
Japan	6 (1.48)
Pakistan	7 (1.48)
Spain	8 (1.48)
United Kingdom	9 (1.48)
Australia and New Zealand	1 (0.74)
Israel	1 (0.74)
Korea	1 (0.74)
Netherlands	1 (0.74)
Singapore	1 (0.74)

Abbreviation: ICU: Intensive care unit.

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Table 2. Characteristics of the panelists

Domain	Frequency (relative to the total domain frequency [%])	Range
Gender		
Male	7 (70)	N/A
Female	3 (30)	
Specialty		
Pulmonology	1 (10)	N/A
Anesthesia and intensivist	1 (10)	
Emergency medicine	2 (20)	
Pharmacotherapy	1 (10)	
Obstetrics and gynecology	1 (10)	
Otorhinolaryngology	1 (10)	
General practice	3 (30)	
Clinical experience (years)		
<10	4 (40)	5 – 35 years
11 – 20	3 (30)	
21 – 30	1 (10)	
>30	2 (20)	
Number of COVID-19 patients visited by the participant		
<50	3 (30)	10 – 2000
50 – 150	4 (40)	
151 – 300	1 (10)	
300 – 450	0	
>450	2 (20)	

creatinine (Cr), serum Cr, GFR, SpO_2, and PaO_2. The critical factors of the six outcomes are displayed in Table 3.

4. Discussion

4.1. Purpose of the study

Due to the complex nature of COVID-19, identifying the effective factors of decision-making for patient outcomes is an essential requirement of the current healthcare systems. Through this survey, the effective factors were identified with a combination of literature review and expert consensus. As patients experience different symptoms after COVID-19 infection, all possible factors should be considered for appropriate treatment and accurate clinical decision-making at each COVID-19 progression stage. Hence, the results were presented based on different stages in the decision-making process.

4.2. Brief information about the key findings

Among the critical factors, SpO_2 was implicated in five out of the six decision-making outcomes for COVID-19 cases. Evidence has revealed that low blood oxygen or hypoxia is a warning sign of severe COVID-19, correlating to the severity of the disease [36]. RR is another critical factor implicated in five out of the six decision-making outcomes, indicating an important role in determining the status of the patients [37].

Several studies have been conducted regarding COVID-19 and the effective risk factors in clinical decision-making. Most of the published studies have focused on specific domains of the patient's condition, whereas different possible aspects of clinical decision-making were considered in the present study. The study by Pijls *et al.* [38] focused solely on the demographic factors influencing the severity of COVID-19. In contrast, we investigated a wide range of clinical factors that could be effective in inpatient assessment.

The results of our study could support the policymakers in preparing the required equipment, such as an oximeter and mechanical ventilation. The oximeter should be accessible for patient monitoring in the ward and at home. In addition, a Bluetooth pulse oximeter with a telehealth system via mobile platforms can be used to check a patient's condition as SpO_2 is a critical factor for decision-making in most domains [39]. Therefore, an effective patient management strategy can be developed by prioritizing the critical factors and subsequently the essential factors.

Medical history was recognized as a critical factor in our survey. Consequently, timely access to the patient's medical records could improve clinical decisions about the patient's condition. Current electronic health records (EHRs) can provide timely information and real-time monitoring for the early detection and management of severe diseases [40]. Given the COVID-19 pandemic, several health-care organizations have rapidly implemented EHRs in their hospitals to improve patient safety management [41,42].

Likewise, the lack of evidence-based recommendations has led to clinicians having to review a vast amount of clinical information just to manage the patients better. Nonetheless, the high rate of infected patients is a major challenge for healthcare providers [43]. In response, several researchers have developed decision-aid tools to address the issue [44,45].

4.3. Recommendations for future studies

This survey could account for the initial step of developing clinical decision support systems (CDSSs) for decision-making based on disease severity to aid physicians in making more accurate decisions within a shorter time [46]. In this regard, Sherimon *et al.* developed a CDSS to combat COVID-19 in primary healthcare to aid clinicians with real-time diagnosis [47]. Despite the effectiveness of such systems, the development process is complex and comprises different stages. Moreover, the early stages of CDSS development commonly involve determining the minimum data sets, as was conducted in this study.

From the point of view of clinical experts, this study investigated the effective demographic and clinical factors of common COVID-19 outcomes. However, this study did not account for cultural and climatic factors that may also effectively affect patient outcomes, warranting further investigation of these factors in future studies.

SARS-CoV-2, the pathogen that causes COVID-19, is still spreading rapidly in many countries around the world. Additionally, there are signs indicating that COVID-19 will become endemic with time but not eradicated. Despite the reduction in the spread of the virus, the identified effective factors may facilitate better management of COVID-19, especially in the upcoming endemic phase, as well as in future pandemics.

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Table 3. The critical factors of six outcomes related to COVID-19 patients

Factors	Decision-making outcomes					
	Length of stay	Ward referrals	Home referrals	Deterioration diagnosis	Discharge	ICU referrals
History of disease (e.g., respiratory diseases, cancer, and chronic diseases)	√	√		√		√
History of immunosuppressive drug use	√					
BMI						√
GFR	√				√	√
CRP	√					
Respiratory rate	√	√		√	√	√
SpO_2 at admission	√	√		√		
PaO_2		√		√		√
SOFA score	√	√				
Venous blood pH				√		
Creatinine						√
D-dimers				√		
SpO_2			√			√

Abbreviations: BMI: Body mass index; CRP: C-reactive protein; GFR: Glomerular filtration rate; ICU: Intensive care unit; PaO_2: Arterial oxygen pressure; SOFA: Sequential organ failure assessment; SpO_2: Oxygen saturation.

This study also demonstrated that relevant information and datasets can be collected and analyzed using data mining methods to determine the predictive factors, thereby highlighting the use of machine learning in future studies.

4.4. Limitations

This study had several limitations. Since this research was conducted during the COVID-19 pandemic, many clinicians opted out of completing the questionnaire due to high stress levels and heavy workloads. For this reason, the number of respondents and participants in this study was limited. Besides that, the clinical experts responded to the questionnaire solely based on their experience with patient management in Iran. In addition, the questionnaire may not be complete as it was prepared without the appropriate factor categorization.

5. Conclusion

The findings of this study could be useful guidance or reference for researchers involved in COVID-19 management studies. The effective factors could be useful for both clinical decision-makers and specialists in health informatics (e.g., design decision-making systems) for the effective management of COVID-19 patients. In practice, our findings could increase awareness among clinical staff regarding the priority of different factors in the decision-making process.

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Conflict of Interest

The authors declare no conflicts of interest with regard to the content presented in this work.

Ethics Approval and Consent to Participate

This work was approved by the Tehran University of Medical Sciences ethics committee with the ethics code: IR.TUMS.VCR.REC.1399.188. Written informed consent was obtained from the participants.

Consent for Publication

Written informed consent was obtained from the participants.

Availability of Data

The minimum datasets questionnaire for COVID-19 decision-making and other relevant data are available from the corresponding author upon reasonable request.

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Appendix

Table A1. Search strategies for each database

Database	Search strategies	Number of studies
PubMed	((“Triage”[Mesh]) OR (“Triage”[Title/Abstract]) OR (“Triages”[Title/Abstract]) OR (“patient classification”[Title/Abstract]) OR (“disease severity”[Title/Abstract]) OR (“disease severity scale”[Title/Abstract])) AND ((“Forecasting”[Mesh]) OR (“Forecasting”[Title/Abstract]) OR (“predict*”[Title/Abstract]) OR (“Prediction”[Title/Abstract]) OR (“scoring system”[Title/Abstract]) OR (“scoring”[Title/Abstract]) OR (“scale”[Title/Abstract])) AND ((“Care Unit, Intensive”[Title/Abstract]) OR (“Care Units, Intensive”[Title/Abstract]) OR (“Intensive Care Unit”[Title/Abstract]) OR (“Unit, Intensive Care”[Title/Abstract]) OR (“Disease Severity”[Title/Abstract]) OR (“Units, Intensive Care”[Title/Abstract]) OR (“Intensive Care Units”[Mesh])) AND ((“severe acute respiratory syndrome coronavirus 2” [Supplementary Concept]) OR (“COVID-19”[Title/Abstract]) OR (“SARS-CoV-2”[Title/Abstract]) OR (“2019 novel coronavirus”[Title/Abstract]) OR (“2019-nCoV”[Title/Abstract]) OR (“Wuhan coronavirus”[Title/Abstract]) OR (“novel coronavirus”[Title/Abstract]))	118
Scopus	(((TITLE-ABS-KEY (triage) OR TITLE-ABS-KEY (“patient classification”) OR TITLE-ABS-KEY (triages))) OR ((TITLE-ABS-KEY (“disease severity”) OR TITLE-ABS-KEY (“disease severity scale”)))) AND ((TITLE-ABS-KEY (forecast*) OR TITLE-ABS-KEY (predict*) OR TITLE-ABS-KEY (prediction) OR TITLE-ABS-KEY (“scoring system”) OR TITLE-ABS-KEY (scoring) OR TITLE-ABS-KEY (scale))) AND ((TITLE-ABS-KEY (“Care Unit, Intensive”) OR TITLE-ABS-KEY (“Care Units, Intensive”) OR TITLE-ABS-KEY (“Intensive Care Unit”) OR TITLE-ABS-KEY (“Unit, Intensive Care”) OR TITLE-ABS-KEY (“Units, Intensive Care”) OR TITLE-ABS-KEY (“Intensive Care Units”))) AND ((TITLE-ABS-KEY (“severe acute respiratory syndrome coronavirus 2”) OR TITLE-ABS-KEY (“COVID-19”) OR TITLE-ABS-KEY (“SARS-CoV-2”) OR TITLE-ABS-KEY (“2019 novel coronavirus”) OR TITLE-ABS-KEY (“2019-nCoV”) OR TITLE-ABS-KEY (“Wuhan coronavirus”) OR TITLE-ABS-KEY (“novel coronavirus”)))	116
Web of Science	1. TS = (“Triage”) OR (“Triages”) OR (“patient classification”) OR (“disease severity”) OR (“disease severity scale”) From 2010 to 2020 2. TS = (“Intensive Care Unit”) OR (“Care Unit, Intensive”) OR (“Intensive Care unit”) OR (“Unit, Intensive Care”) OR (“Units, Intensive Care”) OR (“Care Units, Intensive”) OR (“Intensive Care Units”) 3. TS = (“severe acute respiratory syndrome coronavirus 2”) OR (“COVID-19”) OR (“SARS-CoV-2”) OR (“2019 novel coronavirus”) OR (“2019-nCoV”) OR (“Wuhan coronavirus”) OR (“novel coronavirus”) OR (“coronavirus”) Total=1 AND 2 AND 3	44

Table A2. The contributing factors in clinical decision-making towards the length of hospital stay of COVID-19 patients

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
Demographics and medical history	Age	Age refers to the patient’s age based on the year.	0.4	Essential
	Sex	Sex refers to the gender of the patient.	−0.4	Rejected
	BMI or obesity	BMI is a measure of body fat based on height and weight that applies to adult men and women.	0.4	Essential
	History of diabetes mellitus	Diabetes mellitus is a metabolic disorder characterized by elevated blood sugar levels over a long period [48].	0.6	Essential
	History of cancer or malignancy	Cancer is the abnormal growth of cells. The term malignancy refers to the presence of cancerous cells that can spread to other sites in the body [49,50].	1	Critical
	CVD	CVD is any disease of the heart or any disorder associated with blood vessels [51].	0.8	Critical
	History of renal function impairment or CKD	CKD is the presence of kidney damage or an eGFR of <60 mL/min per 1.73 m^2 for more than two months [52].	0.8	Critical
	History of respiratory disease	The most common respiratory diseases include COPD, asthma, pneumonia, pulmonary fibrosis, and lung cancer [53].	0.8	Critical
	History of liver disease	Liver/hepatic disease is a type of damage to or disease of the liver that can be chronic or acute [54].	0.6	Essential
	History of autoimmune disease	An autoimmune disease refers to any condition in which the immune system mistakenly attacks the body [55].	0.6	Essential
	History of immunosuppressive drug use	Immunosuppressive drugs are a type of drug that suppresses or reduces the strength of the body’s immune system [56].	0.8	Critical
	History of hypertension	Hypertension refers to high blood pressure, which increases the risk of heart disease, stroke, and sometimes death [57].	0.2	Essential
	Other chronic conditions or co-morbidity	Comorbidity is defined as the concurrence of more than one disorder in an individual [58].	0	Essential

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Table A2. (*Continued*)

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
Signs and symptoms	Fever	Fever refers to a high body temperature (over 37.5°C [99.5°F]).	−0.2	Rejected
	Fatigue	Fatigue describes the feeling of tiredness or lack of energy.	0	Essential
	Myalgia and/or arthralgia	Myalgia refers to pain in a muscle or group of muscles. Arthralgia refers to joint stiffness and pain.	−0.2	Rejected
	Vomiting or nausea	Vomiting refers to the excretion of gastric contents through the mouth.	−0.2	Rejected
	Sore throat	A sore throat is the feeling of pain or scratchiness in the throat.	−0.6	Rejected
	RR	RR is one of the main vital signs, referring to the number of breaths a person takes per minute.	0.8	Critical
	Body temperature at admission	Body temperature at admission refers to the patient's body temperature measurement during the first visit.	0	Essential
WBC count	WBC/leukocyte count	Leukocytes play a pivotal role in inflammation and infection [59].	0.2	Essential
	Neutrophil count	Neutrophils are a type of WBC that increase in response to an acute infection [59].	0.2	Essential
	Lymphocyte count	Lymphocytes are a type of WBC with an anti-infection ability and can respond to specific microorganisms [59].	0.4	Essential
	Eosinophil count	Eosinophils are a type of WBC with a histamine-neutralizing effect [59].	−0.8	Rejected
	Monocyte count	Monocytes are a type of WBC that transform into macrophages, which play important roles in both innate and acquired immunities [59].	−0.8	Rejected
Basic metabolic panel	Cr	Cr is an indicator of kidney function [59].	0.6	Essential
	BUN	The nitrogen content of urea is a primary metabolite derived from dietary and tissue proteins [60].	0	Essential
	Glucose	Glucose has a six-carbon structure and is the main source of energy in the body [60].	0	Essential
Cytokines	IL-6	IL-6 is an inflammatory and acute phase response marker [61].	0.2	Essential
Enzymes and biomarkers	Albumin	Albumin is the most abundant protein in blood [60].	−0.6	Rejected
	AST	AST is a good indicator of liver diseases, such as cirrhosis [62].	−0.4	Rejected
	ALT	ALT is an indicator of liver diseases. It is a more specific marker of liver diseases and infection than AST [63].	−0.2	Rejected
	Total bilirubin	Bilirubin is produced in the hemolysis of RBCs [64].	−0.4	Rejected
	LDH	LDH is an enzyme with increased levels of hemolysis, necrosis, pneumonia, and acidosis [65].	0.6	Essential
	CRP	CRP is an indicator of infection and acute inflammation [66].	0.8	Critical
	PCT	PCT is a protein that indicates bacterial infection and sepsis [67].	0	Essential
	Ferritin	Ferritin is an iron-storage protein and an indicator of artery and inflammatory diseases [68].	0.2	Essential
Cardiac biomarkers and tests for the cardiovascular system	Cardiac troponin	Cardiac troponin is the main marker for cardiac infarction [69].	0.4	Essential
	CK	CK is an indicator of muscle, brain, and heart damage [60]	0	Essential
	D-dimers	D-dimers are byproducts of a blood clot and can indicate thrombosis [70].	0.6	Essential
Coagulation screening	AT	AT activity is measured to diagnose thrombotic disorders [71].	0	Essential
	PT	PT measures the function of the external coagulation pathway [60].	0.2	Essential
	APTT	APTT evaluates the internal coagulation pathway [60].	0.4	Essential
	FDPs	FDP measurements indicate fibrinolysis [60].	0.2	Essential
	Fibrinogen	Fibrinogen is a preceding substance that transforms into fibrin [72].	0	Essential
	Platelet count	Platelet count in the blood can cause coagulation formation [59].	0.2	Essential
Other factors	GFR	Indicates the flow of plasma from the glomerulus into Bowman's space in a specific period [73].	1	Critical
	Performance score (e.g., APACHE and ANZROD)	APACHE and ANZROD are different types of illness prognostic scoring systems in intensive care units [74].	0.4	Essential
	SpO_2 at admission	SpO_2 at admission refers to the pulse oximetry-derived SpO_2 in room air at the first hospital admission [36].	1	Critical
	SOFA score	The SOFA score is used as a diagnostic indicator [75].	0.8	Critical
	CURB-65 score	The CURB-65 score is a scoring system that plays a role in patient mortality [76].	0.6	Essential

Abbreviations: ALT: Alanine transaminase; ANZROD: Australian and New Zealand risk of death; APACHE: Acute physiology and chronic health evaluation; APTT: Activated partial thromboplastin time; AST: Aspartate transaminase; AT: Anti-thrombin; BMI: Body mass index; BUN: Blood urea nitrogen; CK: Creatine kinase; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; Cr: Creatinine; CRP: C-reactive protein; CURB-65: Confusion blood urea >42.8 mg/dL, RR>30/min, blood pressure<90/60 mmHg, age>65; CVD: Cardiovascular disease; CVR: Content validity ratio; eGFR: Estimated glomerular filtration rate; FDP: Fibrin degradation product; GFR: Glomerular filtration rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; PCT: Procalcitonin; PT: Prothrombin; RBC: Red blood cell; RR: Respiratory rate; SOFA: Sequential organ failure assessment; SpO_2: Oxygen saturation; WBC: White blood cell.

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Table A3. The contributing factors in clinical decision-making on ward referrals of COVID-19 patients

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
Demographics and medical history	Age	Age refers to the patient's age based on the year.	0.6	Essential
	Sex	Sex refers to the gender of the patient.	−0.8	Rejected
	BMI or obesity	BMI is a measure of body fat based on height and weight that applies to adult men and women.	0.4	Essential
	History of diabetes mellitus	Diabetes mellitus is a metabolic disorder characterized by elevated blood sugar levels over a long period [48].	0.8	Critical
	History of cancer or malignancy	Cancer is the abnormal growth of cells. The term malignancy refers to the presence of cancerous cells that can spread to other sites in the body [49,50].	1	Critical
	History of any CVD	CVD is any disease of the heart or any disorder associated with blood vessels [51].	0.8	Critical
	History of renal function impairment or CKD	CKD is the presence of kidney damage or an eGFR of<60 mL/min/1.73 m^2 for more than 2 months [52].	0.8	Critical
	History of respiratory disease	The most common respiratory diseases include COPD, asthma, pneumonia, pulmonary fibrosis, and lung cancer [53].	1	Critical
	History of liver disease	Liver/hepatic disease is a type of damage to or disease of the liver that can be chronic or acute [54].	0.6	Essential
	History of autoimmune disease	An autoimmune disease refers to any condition in which the immune system mistakenly attacks the body [55].	0.6	Essential
	History of immunosuppressive drug use	Immunosuppressive drugs are a type of drug that suppresses or reduces the strength of the body's immune system [56].	0.6	Essential
	History of hypertension	Hypertension refers to high blood pressure, which increases the risk of heart disease, stroke, and sometimes death [57].	0	Essential
	Other chronic conditions or co-morbidity	Comorbidity is defined as the concurrence of more than one disorder in an individual [58].	0.4	Essential
Signs and symptoms	Fever	Fever refers to a high body temperature (over 37.5°C [99.5°F]).	0.2	Essential
	Fatigue	Fatigue describes the feeling of tiredness or lack of energy.	−0.4	Rejected
	Myalgia and/or arthralgia	Myalgia refers to pain in a muscle or group of muscles. Arthralgia refers to joint stiffness and pain.	−0.6	Rejected
	Vomiting or nausea	Vomiting refers to the excretion of gastric contents through the mouth.	−0.2	Rejected
	Sore throat	A sore throat is the feeling of pain or scratchiness in the throat.	−0.8	Rejected
	RR	RR is one of the main vital signs, referring to the number of breaths a person takes per minute	1	Critical
	Body temperature at admission	Body temperature at admission refers to the patient's body temperature measurement during the first visit.	−0.4	Rejected
WBC count	WBC/leukocyte count	Leukocytes play a pivotal role in inflammation and infection [59].	0.4	Essential
	Neutrophil count	Neutrophils are a type of WBC that increase in response to an acute infection [59].	0.2	Essential
	Lymphocyte count	Lymphocytes are a type of WBC with an anti-infection ability and can respond to specific microorganisms [59].	0.4	Essential
	Eosinophil count	Eosinophils are a type of WBC with a histamine-neutralizing effect [59].	−0.6	Rejected
	Monocyte count	Monocytes are a type of WBC that transform into macrophages, which play important roles in both innate and acquired immunities [59].	−0.6	Rejected
Basic metabolic panel	Cr	Cr is an indicator of kidney function [59].	0.6	Essential
Cytokines	IL-6	IL-6 is an inflammatory and acute phase response marker [61].	0	Essential
Enzymes and biomarkers	Albumin	Albumin is the most abundant protein in blood [60].	−0.4	Rejected
	AST	AST is a good indicator of liver diseases, such as cirrhosis [62].	0	Essential
	ALT	ALT is an indicator of liver diseases. It is a more specific marker of liver diseases and infection than AST [63].	0	Essential

(*Cont'd...*)

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Table A3. (*Continued*)

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
	Total bilirubin	Bilirubin is produced in the hemolysis of RBCs [64].	0	Essential
	LDH	LDH is an enzyme with increased levels of hemolysis, necrosis, pneumonia, and acidosis [65].	0.4	Essential
	CRP	CRP is an indicator of infection and acute inflammation [66].	0.4	Essential
	PCT	PCT is a protein that indicates bacterial infection and sepsis [67].	−0.4	Essential
	Ferritin	Ferritin is an iron-storage protein and an indicator of artery and inflammatory diseases [68].	0	Essential
Cardiac biomarkers and tests for the cardiovascular system	Cardiac troponin	Cardiac troponin is the main marker for cardiac infarction [69]	0.4	Essential
	CK	CK is an indicator of muscle, brain, and heart damage [60].	0.2	Essential
	D-dimers	D-dimers are byproducts of a blood clot and can indicate thrombosis [70].	0.6	Essential
Coagulation screening	Anti-thrombin (AT)	AT activity is measured to diagnose thrombotic disorders [71].	0	Essential
	APTT	APTT evaluates the internal coagulation pathway [60].	0	Essential
	FDPs	FDP measurements indicate fibrinolysis [60].	0.2	Essential
	Fibrinogen	Fibrinogen is a preceding substance that transforms into fibrin [72].	0.2	Essential
Other factors	GFR	Indicates the flow of plasma from the glomerulus into Bowman's space in a specific period [73].	0.6	Essential
	Performance score (e.g., APACHE and ANZROD)	APACHE and ANZROD are different types of illness prognostic scoring systems in intensive care units [74].	0.2	Essential
	SpO_2 at admission	SpO_2 at admission refers to the pulse oximetry-derived SpO_2 in room air at the first hospital admission [36].	0.8	Critical
	SOFA score	The SOFA score is used as a diagnostic indicator [75].	0.6	Essential
	CURB-65 score	The CURB-65 score is a scoring system that plays a role in patient mortality [76].	0.6	Essential
	Blood pH	The pH of blood refers to its acidity. The typical pH of blood in the arteries ranges from 7.35 to 7.45.	0.4	Essential
	PaO_2	PaO_2 refers to the partial pressure of oxygen.	1	Critical

Abbreviations: ALT: Alanine transaminase; ANZROD: Australian and New Zealand risk of death; APACHE: Acute physiology and chronic health evaluation; APTT: Activated partial thromboplastin time; AST: Aspartate transaminase; AT: Anti-thrombin; BMI: Body mass index; CK: Creatine kinase; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; Cr: Creatinine; CRP: C-reactive protein; CURB-65: Confusion, blood urea>42.8 mg/dL, RR>30/min, blood pressure<90/60 mmHg, age>65; CVD: Cardiovascular disease; CVR: Content validity ratio; eGFR: Estimated glomerular filtration rate; FDP: Fibrin degradation product; GFR: Glomerular filtration rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; PaO_2: Arterial oxygen pressure; PCT: Procalcitonin; RBC: Red blood cell; RR: Respiratory rate; SOFA: Sequential organ failure assessment; SpO_2: Oxygen saturation; WBC: White blood cell.

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Table A4. The contributing factors in clinical decision-making on home isolation of COVID-19 patients

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
Demographics and medical history	Age	Age refers to the patient's age based on the year.	0.6	Essential
	Sex	Sex refers to the gender of the patient.	−0.8	Rejected
	BMI or obesity	BMI is a measure of body fat based on height and weight that applies to adult men and women.	0.4	Essential
	History of diabetes mellitus	Diabetes mellitus is a metabolic disorder characterized by elevated blood sugar levels over a long period [48].	0.4	Essential
	History of cancer or malignancy	Cancer is the abnormal growth of cells. The term malignancy refers to the presence of cancerous cells that can spread to other sites in the body [49,50].	0.4	Essential
	History of any CVD	CVD is any disease of the heart or any disorder associated with blood vessels [51].	0.6	Essential
	History of renal function impairment or CKD	CKD is the presence of kidney damage or an eGFR of < 60 mL/min per 1.73 m^2 for more than 2 months [52].	0.2	Essential
	History of respiratory disease	The most common respiratory diseases include COPD, asthma, pneumonia, pulmonary fibrosis, and lung cancer [53].	0.6	Essential
	History of liver disease	Liver/hepatic disease is a type of damage to or disease of the liver that can be chronic or acute [54].	0.2	Essential
	History of autoimmune disease	An autoimmune disease refers to any condition in which the immune system mistakenly attacks the body [55].	0	Essential
	History of immunosuppressive drug use	Immunosuppressive drugs are a type of drug that suppresses or reduces the strength of the body's immune system [56].	0.4	Essential
	History of hypertension	Hypertension refers to high blood pressure, which increases the risk of heart disease, stroke, and sometimes death [57].	−0.2	Rejected
	Other chronic conditions or co-morbidity	Comorbidity is defined as the concurrence of more than one disorder in an individual [58].	0.2	Essential
WBC count	WBC/leukocyte count	Leukocytes play a pivotal role in inflammation and infection [59].	0.6	Essential
	Lymphocyte count	Lymphocytes are a type of WBC with an anti-infection ability and can respond to specific microorganisms [59].	0.4	Essential
Basic metabolic panel	Cr	Cr is an indicator of kidney function [59].	0.6	Essential
Cytokines	IL-6	IL-6 is an inflammatory and acute phase response marker [61].	0	Essential
Enzymes and biomarkers	CRP	CRP is an indicator of infection and acute inflammation [66].	0.4	Essential
	PCT	PCT is a protein that indicates bacterial infection and sepsis [67].	0.2	Essential
	Ferritin	Ferritin is an iron-storage protein and an indicator of artery and inflammatory diseases [68].	0	Essential
Cardiac biomarkers and tests for the cardiovascular system	D-dimers	D-dimers are byproducts of a blood clot and can indicate thrombosis [70].	0.4	Essential
Other factors	GFR	Indicates the flow of plasma from the glomerulus into Bowman's space in a specific period [73].	0.6	Essential
	Performance score (e.g., APACHE and ANZROD)	APACHE and ANZROD are different types of illness prognostic scoring systems in intensive care units [74].	0.6	Essential
	SpO_2	SpO_2 is the percentage of oxygenated hemoglobin in a patient's blood [77].	1	Critical

Abbreviations: ANZROD: Australian and New Zealand Risk of Death; APACHE: Acute physiology and chronic health evaluation; BMI: Body mass index; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; Cr: Creatinine; CRP: C-reactive protein; CVD: Cardiovascular disease; CVR: Content validity ratio; eGFR: Estimated glomerular filtration rate; GFR: Glomerular filtration rate; IL-6: Interleukin-6; PCT: Procalcitonin; SpO_2: Oxygen saturation; WBC: White blood cell.

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Table A5. The contributing factors in the clinical decision-making on deterioration diagnosis of COVID-19 patients

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
Demographics and medical history	Age	Age refers to the patient's age based on the year.	0.4	Essential
	Sex	Sex refers to the gender of the patient.	−0.8	Rejected
	BMI or obesity	BMI is a measure of body fat based on height and weight that applies to adult men and women.	0.4	Essential
	History of diabetes mellitus	Diabetes mellitus is a metabolic disorder characterized by elevated blood sugar levels over a long period [48].	0.6	Essential
	History of cancer or malignancy	Cancer is the abnormal growth of cells. The term malignancy refers to the presence of cancerous cells that can spread to other sites in the body [49,50].	0.4	Essential
	History of any CVD	CVD is any disease of the heart or any disorder associated with blood vessels [51].	0.4	Essential
	History of renal function impairment or CKD	CKD is the presence of kidney damage or an eGFR of < 60 mL/min per 1.73 m^2 for more than 2 months [52].	0.4	Essential
	History of respiratory disease	The most common respiratory diseases include COPD, asthma, pneumonia, pulmonary fibrosis, and lung cancer [53].	0.8	Critical
	History of liver disease	Liver/hepatic disease is a type of damage to or disease of the liver that can be chronic or acute [54].	0	Essential
	History of autoimmune disease	An autoimmune disease refers to any condition in which the immune system mistakenly attacks the body [55].	0.4	Essential
	History of immunosuppressive drug use	Immunosuppressive drugs are a type of drug that suppresses or reduces the strength of the body's immune system [56].	0.4	Essential
	History of hypertension	Hypertension refers to high blood pressure, which increases the risk of heart disease, stroke, and sometimes death [57].	0	Essential
	Other chronic conditions or co-morbidity	Comorbidity is defined as the concurrence of more than one disorder in an individual [58].	0.2	Essential
Signs and symptoms	Fever	Fever refers to a high body temperature (over 37.5°C [99.5°F]).	0.4	Essential
	Fatigue	Fatigue describes the feeling of tiredness or lack of energy.	−0.2	Rejected
	Myalgia and/or arthralgia	Myalgia refers to pain in a muscle or group of muscles. Arthralgia refers to joint stiffness and pain.	−0.2	Rejected
	Vomiting or nausea	Vomiting refers to the excretion of gastric contents through the mouth.	−0.6	Rejected
	Sore throat	A sore throat is the feeling of pain or scratchiness in the throat.	−1	Rejected
	RR	RR is one of the main vital signs, referring to the number of breaths a person takes per minute	1	Critical
	Body temperature at admission	Body temperature at admission refers to the patient's body temperature measurement during the first visit.	0.4	Essential
WBC count	WBC/leukocyte count	Leukocytes play a pivotal role in inflammation and infection [59].	0.4	Essential
	Neutrophil count	Neutrophils are a type of WBC that increase in response to an acute infection [59].	0.2	Essential
	Lymphocyte count	Lymphocytes are a type of WBC with an anti-infection ability and can respond to specific microorganisms [59].	0.4	Essential
	Eosinophil count	Eosinophils are a type of WBC with a histamine-neutralizing effect [59].	−1	Rejected
	Monocyte count	Monocytes are a type of WBC that transform into macrophages, which play important roles in both innate and acquired immunities [59].	−1	Rejected
	Thrombocyte count	Thrombocytosis refers to a higher-than-normal platelet count.	−0.2	Rejected
Basic metabolic panel	Cr	Cr is an indicator of kidney function (59).	0.4	Essential
	BUN	The nitrogen content of urea is a primary metabolite derived from dietary and tissue proteins [60].	0.2	Essential
Cytokines	IL-6	IL-6 is an inflammatory and acute phase response marker [61].	0	Essential
	CD8 cell count	CD8 is a marker of cytotoxic T cells [59].	−0.2	Rejected
	TNF-alpha	TNF-alpha is a proinflammatory pain-causing cytokine [78].	−0.2	Rejected

(*Cont'd...*)

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Table A5. (*Continued*)

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
	IL-1	IL-1 is a costimulatory molecule in the acute phase response [78].	−0.8	Rejected
	IL-2	IL-2 is involved in the proliferation of B-cells and activated T-cells [78].	−0.6	Rejected
	IL-2R	IL-2Rs are neoplasm, autoimmune disorder, and inflammation indicators [78].	−0.6	Rejected
	IL-8	IL-8 is a neutrophil and T-cell chemoattractant [78].	−0.6	Rejected
	IL-10	IL-10 is a cytokine production inhibitor [78].	−0.8	Rejected
Enzymes and biomarkers	Albumin	Albumin is the most abundant protein in blood [60].	−0.2	Rejected
	AST	AST is a good indicator of liver diseases, such as cirrhosis [62].	0	Essential
	ALT	ALT is an indicator of liver diseases. It is a more specific marker of liver diseases and infection than AST [63].	0.2	Essential
	Total bilirubin	Bilirubin is produced in the hemolysis of RBCs [64].	−0.2	Rejected
	LDH	LDH is an enzyme with increased levels of hemolysis, necrosis, pneumonia, and acidosis [65].	0.6	Essential
	CRP	CRP is an indicator of infection and acute inflammation [66].	0.6	Essential
	PCT	PCT is a protein that indicates bacterial infection and sepsis [67].	0.2	Essential
	Ferritin	Ferritin is an iron-storage protein and an indicator of artery and inflammatory diseases [68].	0	Essential
Cardiac biomarkers and tests for the cardiovascular system	Cardiac troponin	Cardiac troponin is the main marker for cardiac infarction [69].	0.6	Essential
	NP-proBNP	NT-proBNP is an essential protein for the production of BNP hormones [79].	0.4	Essential
	CK	CK is an indicator of muscle, brain, and heart damage [60].	−0.2	Rejected
	Myoglobin	Myoglobin is a muscle oxygen storage protein [80].	−0.6	Rejected
	D-dimers	D-dimers are byproducts of a blood clot and can indicate thrombosis [70].	0.8	Critical
Coagulation screening	AT	AT activity is measured to diagnose thrombotic disorders [71].	−0.2	Rejected
	PT	PT measures the function of the external coagulation pathway [60].	−0.2	Rejected
	APTT	APTT evaluates the internal coagulation pathway [60].	−0.2	Rejected
	FDPs	FDP measurements indicate fibrinolysis [60].	0	Essential
	Fibrinogen	Fibrinogen is a preceding substance that transforms into fibrin [72].	−0.2	Rejected
Other factors	Platelet count	Platelet in the blood causes coagulation formation [58].	0.4	Essential
	GFR	Indicates the flow of plasma from the glomerulus into Bowman's space in a specific period [73].	0.4	Essential
	Performance score (e.g., APACHE and ANZROD)	APACHE and ANZROD are different types of illness prognostic scoring systems in intensive care units [74].	0.2	Essential
	SpO_2 at admission	SpO_2 at admission refers to the pulse oximetry-derived SpO_2 in room air at the first hospital admission [36].	1	Critical
	SOFA score	The SOFA score is used as a diagnostic indicator [75].	0.4	Essential
	CURB-65 score	The CURB-65 score is a scoring system that plays a role in patient mortality [76].	0.4	Essential
	Blood pH	The pH of blood refers to its acidity. The typical pH of blood in the arteries ranges from 7.35 to 7.45.	0.8	Critical
	PaO_2	PaO_2 refers to the partial pressure of oxygen.	1	Critical

Abbreviations: ALT: Alanine transaminase; ANZROD: Australian and New Zealand risk of death; APACHE: Acute physiology and chronic health evaluation; APTT: Activated partial thromboplastin time; AST: Aspartate transaminase; AT: Anti-thrombin; BMI: Body mass index; BUN: Blood urea nitrogen; CK: Creatine kinase; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; CURB-65: Confusion, blood urea > 42.8 mg/dL, RR > 30/min, blood pressure < 90/60 mmHg, age > 65; CVD: Cardiovascular disease; CVR: Content validity ratio; eGFR: Estimated glomerular filtration rate; FDP: Fibrin degradation product; GFR: Glomerular filtration rate; IL-1: Interleukin-1; IL-2: Interleukin-2; IL-2R: Interleukin-2R; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; LDH: Lactate dehydrogenase; NP-proBNP: N-terminal pro b-type natriuretic peptide; PaO_2: Arterial oxygen pressure; PCT: Procalcitonin; PT: Prothrombin; RBC: Red blood cell; RR: Respiratory rate; SOFA: Sequential organ failure assessment; SpO_2: Oxygen saturation; TNF-alpha: Tumor necrosis factor-alpha; WBC: White blood cell.

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Table A6. The contributing factors in the clinical decision-making on discharging COVID-19 patients

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
Demographics and medical history	Age	Age refers to the patient's age based on the year.	0.2	Essential
	Sex	Sex refers to the gender of the patient.	−1	Rejected
	BMI or obesity	BMI is a measure of body fat based on height and weight that applies to adult men and women.	0.2	Essential
	History of diabetes mellitus	Diabetes mellitus is a metabolic disorder characterized by elevated blood sugar levels over a long period [48].	0.6	Essential
	History of cancer or malignancy	Cancer is the abnormal growth of cells. The term malignancy refers to the presence of cancerous cells that can spread to other sites in the body [49,50].	0.4	Essential
	History of any CVD	CVD is any disease of the heart or any disorder associated with blood vessels [51].	0.2	Essential
	History of renal function impairment or CKD	CKD is the presence of kidney damage or an eGFR of < 60 mL/min per 1.73 m^2 for more than 2 months [52].	0.4	Essential
	History of respiratory disease	The most common respiratory diseases include COPD, asthma, pneumonia, pulmonary fibrosis, and lung cancer [53].	0.6	Essential
	History of liver disease	Liver/hepatic disease is a type of damage to or disease of the liver that can be chronic or acute [54].	0.2	Essential
	History of autoimmune disease	An autoimmune disease refers to any condition in which the immune system mistakenly attacks the body [55].	0.2	Essential
	History of immunosuppressive drug use	Immunosuppressive drugs are a type of drug that suppresses or reduces the strength of the body's immune system [56].	0.6	Essential
	History of hypertension	Hypertension refers to high blood pressure, which increases the risk of heart disease, stroke, and sometimes death [57].	0	Essential
	Other chronic conditions or co-morbidity	Comorbidity is defined as the concurrence of more than one disorder in an individual [58].	0.2	Essential
Signs and symptoms	Fever	Fever refers to a high body temperature (over 37.5°C [99.5°F]).	0.4	Essential
	Fatigue	Fatigue describes the feeling of tiredness or lack of energy.	−0.4	Rejected
	Myalgia and/or arthralgia	Myalgia refers to pain in a muscle or group of muscles. Arthralgia refers to joint stiffness and pain.	−0.8	Rejected
	Vomiting or nausea	Vomiting refers to the excretion of gastric contents through the mouth.	0	Essential
	Sore throat	A sore throat is the feeling of pain or scratchiness in the throat.	−1	Rejected
	RR	RR is one of the main vital signs, referring to the number of breaths a person takes per minute	1	Critical
	Body temperature at admission	Body temperature at admission refers to the patient's body temperature measurement during the first visit.	−0.6	Rejected
WBC count	WBC/leukocyte count	Leukocytes play a pivotal role in inflammation and infection [59].	0.6	Essential
	Neutrophil count	Neutrophils are a type of WBC that increase in response to an acute infection [59].	0	Essential
	Lymphocyte count	Lymphocytes are a type of WBC with an anti-infection ability and can respond to specific microorganisms [59].	0.6	Essential
	Eosinophil count	Eosinophils are a type of WBC with a histamine-neutralizing effect [59].	−0.8	Rejected
	Monocyte count	Monocytes are a type of WBC that transform into macrophages, which play important roles in both innate and acquired immunities [59].	−0.8	Rejected
	Thrombocyte count	Thrombocytosis refers to a higher-than-normal platelet count.	−0.2	Rejected
Basic metabolic panel	BUN	The nitrogen content of urea is a primary metabolite derived from dietary and tissue proteins [60].	0.4	Essential
Cytokines	IL-6	IL-6 is an inflammatory and acute phase response marker [61].	0	Essential
	TNF-alpha	TNF-alpha is a proinflammatory pain-causing cytokine [78].	0	Essential
	IL-8	IL-8 is a neutrophil and T-cell chemoattractant [78].	−0.4	Rejected
Enzymes and biomarkers	Albumin	Albumin is the most abundant protein in blood [60].	−0.6	Rejected
	LDH	LDH is an enzyme with increased levels of hemolysis, necrosis, pneumonia, and acidosis [65].	0.4	Essential
	CRP	CRP is an indicator of infection and acute inflammation [66].	−0.2	Rejected

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Table A6. (*Continued*)

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
	PCT	PCT is a protein that indicates bacterial infection and sepsis [67].	0.2	Essential
	Ferritin	Ferritin is an iron-storage protein and an indicator of artery and inflammatory diseases [68].	−0.2	Rejected
Cardiac biomarkers and tests for the cardiovascular system	Cardiac troponin	Cardiac troponin is the main marker for cardiac infarction [69]	0.4	Essential
	D-dimers	D-dimers are byproducts of a blood clot and can indicate thrombosis [70].	0.6	Essential
Coagulation screening	AT	AT activity is measured to diagnose thrombotic disorders [71].	−0.2	Rejected
	PT	PT measures the function of the external coagulation pathway [60].	0	Essential
	Fibrinogen	Fibrinogen is a preceding substance that transforms into fibrin [72].	0	Essential
Other factors	GFR	Indicates the flow of plasma from the glomerulus into Bowman's space in a specific period [73].	0.8	Critical
	SpO_2 at admission	SpO_2 at admission refers to the pulse oximetry-derived SpO_2 in room air at the first hospital admission [36].	0.2	Essential
	CURB-65 score	The CURB-65 score is a scoring system that plays a role in patient mortality [76].	0.4	Essential

Abbreviations: AT: Anti-thrombin; BMI: Body mass index; BUN: Blood urea nitrogen; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; CURB-65: Confusion, blood urea > 42.8 mg/dL, RR > 30/min, blood pressure < 90/60 mmHg, age > 65; CVD: Cardiovascular disease; CVR: Content validity ratio; eGFR: Estimated glomerular filtration rate; GFR: Glomerular filtration rate; IL-6: Interleukin-6; IL-8: Interleukin-8; LDH: Lactate dehydrogenase; PCT: Procalcitonin; PT: Prothrombin; RR: Respiratory rate; SpO_2: Oxygen saturation; TNF-alpha: Tumor necrosis factor-alpha; WBC: White blood cell.

Table A7. The contributing factors in clinical decision-making on ICU referrals of COVID-19 patients

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
Demographics and medical history	Age	Age refers to the patient's age based on the year.	0.4	Essential
	Sex	Sex refers to the gender of the patient.	−1	Rejected
	BMI or obesity	BMI is a measure of body fat based on height and weight that applies to adult men and women.	0.8	Critical
	History of diabetes mellitus	Diabetes mellitus is a metabolic disorder characterized by elevated blood sugar levels over a long period [48].	0.4	Essential
	History of cancer or malignancy	Cancer is the abnormal growth of cells. The term malignancy refers to the presence of cancerous cells that can spread to other sites in the body [49,50].	0.8	Critical
	History of any CVD	CVD is any disease of the heart or any disorder associated with blood vessels [51].	0.4	Essential
	History of renal function impairment or CKD	CKD is the presence of kidney damage or an eGFR of < 60 mL/min per 1.73 m^2 for more than 2 months [52].	1	Critical
	History of respiratory disease	The most common respiratory diseases include COPD, asthma, pneumonia, pulmonary fibrosis, and lung cancer [53].	1	Critical
	History of liver disease	Liver/hepatic disease is a type of damage to or disease of the liver that can be chronic or acute [54].	0.6	Essential
	History of autoimmune disease	An autoimmune disease refers to any condition in which the immune system mistakenly attacks the body [55].	0.6	Essential
	History of immunosuppressive drug use	Immunosuppressive drugs are a type of drug that suppresses or reduces the strength of the body's immune system [56].	0.2	Essential
	History of hypertension	Hypertension refers to high blood pressure, which increases the risk of heart disease, stroke, and sometimes death [57].	0	Essential
	Other chronic conditions or co-morbidity	Comorbidity is defined as the concurrence of more than one disorder in an individual [58].	0.4	Essential
Signs and symptoms	RR	RR is one of the main vital signs, referring to the number of breaths a person takes per minute	0.8	Critical
	Body temperature at admission	Body temperature at admission refers to the patient's body temperature measurement during the first visit.	−0.4	Rejected

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Table A7. (*Continued*)

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
WBC count	WBC/leukocyte count	Leukocytes play a pivotal role in inflammation and infection [59].	0.4	Essential
	Neutrophil count	Neutrophils are a type of WBC that increase in response to an acute infection [59].	0	Essential
	Lymphocyte count	Lymphocytes are a type of WBC with an anti-infection ability and can respond to specific microorganisms [59].	0.4	Essential
	Eosinophil count	Eosinophils are a type of WBC with a histamine-neutralizing effect [59].	−0.4	Rejected
	Monocyte count	Monocytes are a type of WBC that transform into macrophages, which play important roles in both innate and acquired immunities [59].	-0.6	Rejected
Basic metabolic panel	Cr	Cr is an indicator of kidney function [59].	0.8	Critical
	BUN	The nitrogen content of urea is a primary metabolite derived from dietary and tissue proteins [60].	0	Essential
	Glucose	Glucose has a six-carbon structure and is the main source of energy in the body [60].	0	Essential
Cytokines	IL-6	IL-6 is an inflammatory and acute phase response marker [61].	0	Essential
	CD8 cell count	CD8 is a marker of cytotoxic T cells [59].	−0.4	Rejected
	TNF-alpha	TNF-alpha is a proinflammatory pain-causing cytokine [78].	−0.2	Rejected
	IL-1	IL-1 is a costimulatory molecule in the acute phase response [78].	−0.6	Rejected
	IL-2	IL-2 is involved in the proliferation of B-cells and activated T-cells [78].	−0.8	Rejected
	IL-2R	IL-2Rs are neoplasm, autoimmune disorder, and inflammation indicators [78].	−0.8	Rejected
	IL-8	IL-8 is a neutrophil and T-cell chemoattractant [78].	−0.6	Rejected
	IL-10	IL-10 is a cytokine production inhibitor [78].	−0.8	Rejected
Enzymes and biomarkers	Albumin	Albumin is the most abundant protein in blood [60].	−0.4	Rejected
	AST	AST is a good indicator of liver diseases, such as cirrhosis [62].	0	Essential
	ALT	ALT is an indicator of liver diseases. It is a more specific marker of liver diseases and infection than AST [63].	0	Essential
	Total bilirubin	Bilirubin is produced in the hemolysis of RBCs [64].	−0.4	Rejected
	LDH	LDH is an enzyme with increased levels of hemolysis, necrosis, pneumonia, and acidosis [65].	1	Critical
	Serum Cr	A serum (blood) Cr test is a blood test used to evaluate the efficiency of the kidney for blood filtration.	0.4	Essential
	CRP	CRP is an indicator of infection and acute inflammation [66].	0.2	Essential
	PCT	PCT is a protein that indicates bacterial infection and sepsis [67].	−0.2	Rejected
	Ferritin	Ferritin is an iron-storage protein and an indicator of artery and inflammatory diseases [68].	−0.2	Rejected
Cardiac biomarkers and tests for the cardiovascular system	Cardiac troponin	Cardiac troponin is the main marker for cardiac infarction [69]	0.2	Essential
	CK	CK is an indicator of muscle, brain, and heart damage [60].	−0.2	Rejected
	D-dimers	D-dimers are byproducts of a blood clot and can indicate thrombosis [70].	0.2	Essential
	Myoglobin	Myoglobin is a muscle oxygen storage protein [80].	−0.4	Rejected
Coagulation screening	AT	AT activity is measured to diagnose thrombotic disorders [71].	−0.2	Rejected
	PT	PT measures the function of the external coagulation pathway [60].	−0.2	Rejected
	APTT	APTT evaluates the internal coagulation pathway [60].	−0.2	Rejected
	FDPs	FDP measurements indicate fibrinolysis [60].	−0.4	Rejected
	Fibrinogen	Fibrinogen is a preceding substance that transforms into fibrin [72].	−0.2	Rejected
Other factors	GFR	Indicates the flow of plasma from the glomerulus into Bowman's space in a specific period [73].	1	Critical
	Performance score (e.g., APACHE and ANZROD)	APACHE and ANZROD are different types of illness prognostic scoring systems in ICUs [74].	0.2	Essential
	SpO_2	SpO_2 is the percentage of oxygenated hemoglobin in a patient's blood [77].	0.8	Critical
	Sequential organ failure assessment (SOFA) score	The SOFA score is used as a diagnostic indicator [75].	0.4	Essential

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Table A7. (*Continued*)

Factors	Data set	Definition	CVR	CVR assessment (critical, essential, or rejected)
	CURB-65 score	The CURB-65 score is a scoring system that plays a role in patient mortality [76].	0.4	Essential
	Blood pH	The pH of blood refers to its acidity. The typical pH of blood in the arteries ranges from 7.35 to 7.45.	0.6	Essential
	PaO_2	PaO_2 refers to the partial pressure of oxygen.	1	Critical

Abbreviations: ALT: Alanine transaminase; ANZROD: Australian and New Zealand risk of death; APACHE: Acute physiology and chronic health evaluation; APTT: Activated partial thromboplastin time; AST: Aspartate transaminase; AT: Anti-thrombin; BMI: Body mass index; BUN: Blood urea nitrogen; CK: Creatine kinase; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; Cr: Creatinine; CRP: C-reactive protein; CURB-65: Confusion, blood urea > 42.8 mg/dL, RR > 30/min, blood pressure < 90/60 mmHg, age > 65; CVD: Cardiovascular disease; CVR: Content validity ratio; eGFR: Estimated glomerular filtration rate; FDP: Fibrin degradation product; GFR: Glomerular filtration rate; IL-1: Interleukin-1; IL-2: Interleukin-2; IL-2R: Interleukin-2R; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; LDH: Lactate dehydrogenase; PaO_2: Arterial oxygen pressure; PCT: Procalcitonin; PT: Prothrombin; RBC: Red blood cell; RR: Respiratory rate; SOFA: Sequential organ failure assessment; SpO_2: Oxygen saturation; TNF-alpha: Tumor necrosis factor-alpha; WBC: White blood cell; ICU: Intensive care unit.

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ORIGINAL ARTICLE

Emotional repression in patients with chronic inflammatory rheumatism

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Abstract:

Background: A person's psychological background may support and direct the inflammatory evolution of a disease toward a specific type of chronic inflammatory rheumatism (CIR).
Aim: This study aimed to identify a particular emotional profile of patients with CIR, particularly rheumatoid arthritis (RA) and spondyloarthritis (SpA), based on psychological profile assessments between patients with and without CIR. Emotional repression, that is, a tendency to inhibit the expression of negative feelings and/or unpleasant thoughts, was particularly studied.
Methods: This monocentric observational pilot study included patients from the rheumatology department of a university hospital. These patients were systematically assessed for different psychological parameters by an experienced psychiatrist, and their clinical and biological characteristics were collected accordingly. Data analysis was performed using the Chi-squared test or Fisher's exact test.
Results: Fifty-nine patients were assessed: 47 patients with CIR (i.e., 27 with RA and 20 with SpA) (CIR group) and 12 non-CIR patients (i.e., nine with osteoarthritis, one with viral disease, one with osteoporosis, and one with osteomalacia) (control group). Severe emotional repression and early life events were both significantly higher in the CIR group than in the control group ($P = 0.02$). In contrast, severe psychological and somatic complaints were significantly higher in the control group than in the CIR group ($P < 0.01$ and $P = 0.01$, respectively).
Conclusion: Our findings suggested that emotional repression from traumatic life events could aggravate the etiology and/or course of CIR. Therefore, appropriate psychological care should have a relevant place within the current therapeutic options for the clinical management of CIR.
Relevance for Patients: The management of CIR should include psychological support as learning coping mechanisms can facilitate the recovery of CIR patients.

1. Introduction

The development of chronic inflammatory rheumatism (CIR) is multi-factorial (e.g., genetic, environmental, hormonal, infectious, and/or psychological), and the degree of implication of these different factors in CIR onset has not been determined [1,2]. Several studies on traumatic life events and stressful situations have suggested that such situations could be implicated in triggering CIR onset and its symptomatic progression [3,4].

Non-pharmacological interventions have recently been used more frequently for disease management, especially regular physical activity, educational therapeutic workshops with support groups, and mindfulness meditation, among others. In addition, self-reported evaluation and patient-reported outcomes have become increasingly important for the assessment of diseases, suggesting that the patients' psychological well-being is essential in routine practice for rheumatologists to evaluate the efficacy of disease management

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with better precision [5]. Likewise, psychological support is increasingly integrated into the management of patients with CIR as they are more prone to mental and overall health disorders.

Emotional repression refers to the tendency to inhibit the expression of negative feelings and/or unpleasant thoughts and is a common manifestation in CIR patients. Hence, an assessment of the patients' emotional profile could provide a more relevant and effective approach to managing emotional repression and treating CIR. In this regard, we hypothesized that a particular psychological profile, namely, emotional repression, could be associated with autoimmune deregulation.

Herein, this preliminary and exploratory study primarily investigated the emotional function of CIR patients by assessing their psychological profiles to explore a possible association between autoimmunity and emotional regulation. In addition, we further evaluated the emotional profiles for potential associations with other conditions (i.e., rheumatoid arthritis [RA] and spondyloarthritis [SpA]) and different rheumatological characteristics (i.e., biological inflammatory syndrome, sacroiliitis, structural involvement (i.e., osteoarticular destruction of the joint due to the inflammatory activity of rheumatism), and positive rheumatoid factor [RF], anti-citrullinated peptide antibody [ACPA], and human leukocyte antigen *[HLA]-B27* allele).

2. Methods

2.1. Population and study design

This monocentric cross-sectional observational pilot study was conducted in the rheumatology department of a university hospital. During a routine follow-up, the CIR patients were offered an evaluation based on the global CIR management framework, which included dermatological, dental, and gynecological consultations, as well as rheumatologist-requested psychiatric assessments (anxiety disorders, depressive disorders, sleep disorders, conjugal violence, and childhood traumas). None of the recruited 59 patients refused to participate in the evaluation. The exclusion criteria were: age <18 or >65 years old, cognitive disorders, substance dependence, or acute somatic or any psychiatric disorders requiring emergency hospitalization.

The participating patients were accompanied to the rheumatology department by seven different rheumatologists. CIR patients were classified as having RA (based on the 2010 classification by the American College of Rheumatology/European League Against Rheumatism) SpA (based on the 2009 criteria by the Assessment of SpA International Society), or psoriatic arthritis (based on the ClASsification criteria for Psoriatic ARthritis [CASPAR]). We identified 12 patients with ankylosing SpA and eight with psoriatic arthritis, and these patients were categorized under SpA to facilitate statistical analyses. Although their clinical characteristics might differ slightly, their pathologies share common pathophysiological mechanisms and genetic backgrounds, such as the presence of *HLA-B27*.

Non-CIR patients constituted the control group, and these patients were in the rheumatology department for other rheumatological diseases.

2.2. Psychological assessment tools

An experienced psychiatrist collected information during a semi-structured, semi-directed interview lasting 1.5 – 2 h. The psychological parameters assessed were (i) depressive symptoms and their severity (based on the Montgomery-Asberg Depression Rating Scale) [6]; (ii) history of major depression episodes; (iii) anxiety symptoms using a 21-question multiple-choice self-report inventory (i.e., the Beck Anxiety Inventory) [7]; (iv) alexithymia, a behavioral trait of individuals who are unable to identify and describe their interior feelings, have limited imaginative capacity, and tend to focus their thoughts externally rather than resorting to introspection [8,9], and its severity using the 20-item Toronto Alexithymia Scale [10]; (v) social desirability intensity, that is, the tendency to seek approval of others and preserve one's self-image, using the Marlowe-Crowne Social Desirability scale (MCSD), a 33-item self-report questionnaire [11]; (vi) the severity of emotional repression, that is, the tendency to inhibit the expression of negative feelings or disagreeable thoughts, in accordance with the Weinberger classification; and (vii) the combination of State-Trait Anxiety Inventory (STAI) [12] and MCSD as emotionally repressed individuals typically have a low STAI score and high MCSD.

The psychiatrist used a Likert-type scale to assess the severity of the psychological parameters in a specific questionnaire, which assessed (i) the severity of somatic and psychological complaints (i.e., severe complaints referred to personalized responses to most of the questions); (ii) emotional-expressivity intensity (i.e., graded as "mild" when the patient had several emotional moments without excessive reactions, "moderate" when the patient's facial expressions were accompanied by fluctuating emotions as the discussion progressed, or "severe" when the patient had a tendency for hyper-expressivity throughout the interview); (iii) life events (i.e., type 1 for events occurring before 15 years old and type 2 for events occurring within 3 years preceding the rheumatological disease onset) and their intensities (i.e., classified as "mild" when stressful events were non-existent or mild, "moderate" when stressful events did not incur traumatic stress [e.g., emotional deprivation concerning socio-economic difficulties, severe or disabling diseases of close friends/relatives], or "severe" for a traumatic event [e.g., sudden death of a person caring for a child, physical or sexual assault, patient witnessed a death, or thought he/she would die]); (iv) somatic escalation (i.e., the occurrence of a series of several somatic disorders or another chronic pathology before disease onset); (v) actual stress level; (vi) impact of the rheumatological disease on the patient's professional activities, corresponding to the occupational repercussions experienced (i.e., classified as "mild" for minor impact, "moderate" for notable impact, or "severe" for a painful experience [e.g., loss of professional environment and activity, feeling of injustice, or elevated fear of losing one's job]); (vii) manual labor; and (viii) physical activity enjoyment before and after disease onset.

For the different psychological parameters, we combined the "mild" and "moderate" intensities for comparison against the "severe" intensity. The mild-to-moderate psychological disorders

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were easily identified in patients exhibiting severe anxiety or depressive comorbidities and emotional experiences (often affected by chronic pain), but retaining the "severe" intensity enabled a more significant difference. In addition, this approach accounted for the population recruitment bias.

During the same hospitalization, various patient characteristics, mostly rheumatological, were collected from the electronic medical files using the *DxCare* (medical information and prescription software) program. The collected data included: (i) Biological inflammatory syndrome, defined as an erythrocyte sedimentation rate ≥30 mm/1st h and/or C-reactive protein ≥5 mg/L; (ii) positive ACPA, defined as 7 U/mL by enzyme-linked immunosorbent assay (ELISA); (iii) RF >15 IU/mL by ELISA; (iv) magnetic resonance imaging (MRI) detection of grade-2 bilateral or grade-3 unilateral sacroiliitis, with active inflammatory (edema) or chronic (erosion, bone condensation, bone bridges, and fat conversion) lesions.

2.3. Statistical analysis

Continuous variables were expressed as median (first quartile [Q1] – third quartile [Q3]). Categorical variables were expressed as number (percentages), where the percentages were calculated after excluding missing data, and were compared by Chi-squared test or Fisher's exact test accordingly. Missing data were not replaced. For all analyses, $P < 0.05$ was considered statistically significant. Type I error was not adjusted for multiplicity because of the exploratory character of the comparisons. All statistical analyses were performed with SAS release 9.4 (SAS Institute Inc, USA).

3. Results

3.1. Patient characteristics

The study population comprised 59 patients: 47 (79.7 %) CIR patients and 12 (20.3%) non-CIR patients. The patients' characteristics according to their disease are summarized in Table 1.

The control group consisted of 12 women with a median age of 65.0 years [55.0 – 72.0] (nine with osteoarthritis, one with viral disease, one with osteoporosis, and one with osteomalacia). In addition, the nine women with osteoarthritis had structural involvement.

Among the 47 CIR patients (72.3% women and 27.7% men; median age 55.0 years [39.0 – 60.0]), 27 (57.4%) had RA and 20 (42.6%) had SpA. Among the 27 RA patients (81.5% women median age 57 years [52 – 63]), most were RF-positive, ACPA-positive, and had structural involvement. In addition, 10 of the RA patients had biological inflammatory syndrome. Among the 20 SpA patients (60.0% women; median age 41.5 years [34.5 – 53.0]), six of them had a biological inflammatory syndrome, nine of them were *HLA-B27*-positive, and 11 of them had MRI-detected sacroiliitis.

3.2. Psychological assessments

A comparison between the CIR and control groups displayed significant differences in emotional repression, somatic complaints, psychological complaints, type-1 life-event severity, manual labor, or physical activity enjoyment before disease diagnosis (Table 2).

A comparison of the RA and SpA groups revealed significant differences in prior depressive episodes, professional impact, and manual labor (Table 3).

A comparison between patients with and without biological inflammatory syndromes revealed significant differences in emotional repression (Table 4).

A comparison between patients with and without structural involvement revealed significant differences in somatic complaints, emotional expressivity, professional impact, and physical activity enjoyment before disease onset (Table 5).

In addition, none of the psychological parameters were significantly associated with ACPA. Likewise, the number of patients who were *HLA-B27*-positive or had sacroiliitis was too low for analysis. Hence, their significance and association could not be established.

4. Discussion

The objective of this study was to assess the relevance of psychological support for patients with CIR. CIR patients, compared to those with other rheumatological pathologies, presented significantly more frequent severe emotional repression, whereas those with other pathologies had significantly more frequent severe psychological and somatic complaints, potentially attesting to their strong emotional repression.

Table 1. Patients' characteristics according to their disease (*n*=59)

Characteristics	RA (*n*=27)	SpA (*n*=20)	CIR (*n*=47)	Other diseases (*n*=12)
Median age [Q1 – Q3] (yr)	57.0 [52.0 – 63.0]	41.5 [34.5 – 53.0]	55.0 [39.0 – 60.0]	65.0 [55.0 – 72.0]
F/M sex ratio	22/5	12/8	34/13	12/0
Rheumatoid factor+, *n* (%)	18 (66.7)	1 (12.5)	19 (54.3)	0 (0)
ACPA+, *n* (%)	17 (63)	1 (12.5)	18 (51.4)	0 (0)
Elevated ESR and/or CRP, *n* (%)	10 (37.0)	6 (30)	16 (34.0)	0 (0)
HLA-B27+, *n* (%)	0 (0)	9 (47.4)	9 (42.9)	0 (0)
Sacroiliitis, *n* (%)	0 (0)	10 (55.6)	10 (50)	0 (0%)
Structural involvement, *n* (%)	14 (51.9)	0 (0)	14 (35)	9 (81.8)

Note: CIR refers to the combination of RA and SpA.

Abbreviation: +: Positive; ACPA: Anti-citrullinated peptide antibody; CIR: Chronic inflammatory rheumatism; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; F/M: Female-to-male; *HLA-B27*: Human leukocyte antigen B27; Q1: First quartile; Q3: Third quartile; RA: Rheumatoid arthritis; SpA: Spondyloarthritis; yr: Year.

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Table 2. Psychological assessments of patients with CIR versus other diseases

Psychological parameters	CIR (*n*=47)	Other diseases (*n*=12)	*P*-value
Depression	38 (80.9%)	11 (91.7%)	0.67
Depression intensity			0.4
Mild/moderate	32 (84.2%)	8 (72.7%)	
Severe	6 (15.8%)	3 (27.3%)	
Previous depression	37 (78.7%)	11 (91.7%)	0.431
Anxiety	47 (100%)	12 (100%)	NA
Anxiety intensity			0.174
Mild/moderate	21 (44.7%)	8 (66.7%)	
Severe	26 (55.3%)	4 (33.3%)	
Alexithymia	46 (97.9%)	11 (91.7%)	0.368
Alexithymia intensity			1
Mild/moderate	20 (43.5%)	5 (45.5%)	
Severe	26 (56.5%)	6 (54.5%)	
Social desirability			0.431
Mild/moderate	37 (78.7%)	11 (91.7%)	
Severe	10 (21.3%)	1 (8.3%)	
Emotional repression			0.019*
Mild/moderate	25 (53.2%)	11 (91.7%)	
Severe	22 (46.8%)	1 (8.3%)	
Conflict-management style			0.716
Avoidance	37 (78.7%)	9 (75%)	
Intermediate	10 (21.3%)	3 (25%)	
Tendency to cede responsibility to others			0.501
Mild/moderate	45 (95.7%)	11 (91.7%)	
Severe	2 (4.3%)	1 (8.3%)	
Persecution complex	14 (29.8%)	1 (8.3%)	0.16
Somatic complaints			0.01*
Mild/moderate	32 (68.1%)	3 (25%)	
Severe	15 (31.9%)	9 (75%)	
Psychological complaints			0.002*
Mild/moderate	33 (70.2%)	2 (16.7%)	
Severe	14 (29.8%)	10 (83.3%)	
Emotional expressivity intensity			1
Mild/moderate	32 (68.1%)	8 (66.7%)	
Severe	15 (31.9%)	4 (33.3%)	
Life event 1	29 (65.9%)	8 (72.7%)	1
Life event 1 intensity			0.015*
Mild/moderate	15 (51.7%)	8 (100%)	
Severe	14 (48.3%)	0 (0%)	
Life event 2	44 (93.6%)	11 (91.7%)	1
Life event 2 intensity			1
Mild/moderate	30 (68.2%)	8 (72.7%)	
Severe	14 (31.8%)	3 (27.3%)	
Heavy conflictual load over the last 3 years	40 (85.1%)	9 (75.0%)	0.409
Somatic escalade	14 (29.8%)	7 (58.3%)	0.093
Actual stress level			1
Mild/moderate	44 (93.6%)	12 (100%)	
Severe	3 (6.4%)	0 (0%)	
Professional impact			0.064
Mild/moderate	22 (50%)	7 (87.5%)	
Severe	22 (50%)	1 (12.5%)	
Manual labor	28 (59.6%)	2 (16.7%)	0.008*
Physical activity enjoyment pre-diagnosis	23 (48.9%)	2 (16.7%)	0.043*
Physical activity enjoyment post-diagnosis	8 (17%)	1 (8.3%)	0.67

Note: Data are expressed as *n* (%) and compared using the Chi-squared test or Fisher's exact test accordingly; *$P<0.05$.
Abbreviations: NA: Not applicable; CIR: Chronic inflammatory rheumatism.

Temoshok [13] previously described the personality profile of RA patients as type C, characterized by submissive behavior, conciliatory approach, repression of hostility, self-effacement of personal needs, and depressive vulnerability. Grossarth-Maticek *et al.* [14,15] made similar observations in cancer patients. Bayle *et al.* [16] devised a psychological vulnerability score and obtained converging results close to the type C personality, and the scores were significantly higher for patients with secondary Raynaud's syndrome than a control group with idiopathic or primary Raynaud's syndrome.

Nagano *et al.* [17] demonstrated that rational and anti-emotional behaviors by RA patients, characterized by an extreme tendency to squelch emotional behaviors and rationalize negative experiences, were associated with poorer prognoses. Ishii *et al.* [18] found that RA patients, who were easily brought to tears in response to stress, had better responses to treatment and better overall prognoses.

Collectively, previous studies and our present findings highlight the importance of emotional dysregulation, especially emotional repression, on CIR etiology and prognosis. However, the present study should not be generalized as biased toward CIR or propose a secondary coping strategy for CIR. Emotional repression has also been considered a consequence of the CIR diagnosis instead of CIR itself [19,20].

The intensity of key early life events was significantly more severe for CIR patients than for those with other diseases. Cutolo and Straub [21,22] reported that stressful events preceded RA onset for 86% of their patients.

Several studies have associated severe life events with CIR onset or flares, whereas other studies have associated CIR with minor life events and daily stress. In contrast, we found no significant difference in the actual stress level presented by CIR and other diseases, probably because of a lack of statistical power. Rimón and Laasko [23] described that higher stress at RA onset predicted a poorer prognosis for the disease. O'Donovan *et al.* [24] also found that veterans experiencing trauma and

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Table 3. Psychological assessments of patients with RA versus SpA

Psychological parameters	RA (*n*=27)	SpA (*n*=20)	*P*-value
Depression	21 (77.8%)	17 (85%)	0.713
Depression intensity			0.197
Mild/moderate	16 (76.2%)	16 (94.1%)	
Severe	5 (23.8%)	1 (5.9%)	
Previous depression	26 (96.3%)	11 (55%)	<0.001*
Anxiety	27 (100%)	20 (100%)	NA
Anxiety intensity			0.069
Mild/moderate	9 (33.3%)	12 (60.0%)	
Severe	18 (66.7%)	8 (40.0%)	
Alexithymia	27 (100%)	19 (95%)	0.426
Alexithymia intensity			0.172
Mild/moderate	14 (51.9%)	6 (31.6%)	
Severe	13 (48.1%)	13 (68.4%)	
Social desirability			0.481
Mild/moderate	20 (74.1%)	17 (85%)	
Severe	7 (25.9%)	3 (15%)	
Emotional repression			0.333
Mild/moderate	16 (59.3%)	9 (45%)	
Severe	11 (40.7%)	11 (55%)	
Conflict-management style			0.481
Avoidance	20 (74.1%)	17 (85%)	
Intermediate	7 (25.9%)	3 (15%)	
Tendency to cede responsibility to others			0.5
Mild/moderate	25 (92.6%)	20 (100%)	
Severe	2 (7.4%)	0 (0%)	
Persecution complex	10 (37%)	4 (20%)	0.207
Somatic complaints			0.381
Mild/moderate	17 (63%)	15 (75%)	
Severe	10 (37%)	5 (25%)	
Psychological complaints			0.207
Mild/moderate	17 (63%)	16 (80%)	
Severe	10 (37%)	4 (20%)	
Emotional expressivity intensity			0.132
Mild/moderate	16 (59.3%)	16 (80%)	
Severe	11 (40.7%)	4 (20%)	
Life event 1	16 (66.7%)	13 (65%)	0.908
Life event 1 intensity			0.837
Mild/moderate	8 (50%)	7 (53.8%)	
Severe	8 (50%)	6 (46.2%)	
Life event 2	24 (88.9%)	20 (100%)	0.251
Life event 2 intensity			0.375
Mild/moderate	15 (62.5%)	15 (75%)	
Severe	9 (37.5%)	5 (25%)	
Heavy conflictual load over the last three years	22 (81.5%)	18 (90%)	0.682
Somatic escalade	6 (22.2%)	8 (40%)	0.188
Actual stress level			0.251
Mild/moderate	24 (88.9%)	20 (100%)	
Severe	3 (11.1%)	0 (0%)	
Professional impact			0.006*
Mild/moderate	17 (68%)	5 (26.3%)	
Severe	8 (32%)	14 (73.7%)	
Manual labor	12 (44.4%)	16 (80%)	0.014*
Physical activity enjoyment pre-diagnosis	10 (37%)	13 (65%)	0.058
Physical activity enjoyment post-diagnosis	5 (18.5%)	3 (15%)	1

(Cont'd...)

Table 3. *(Continued)*

Note: Data are expressed as *n* (%) and compared using the Chi-squared test or Fisher's exact test accordingly; *$P<0.05$.

Abbreviations: NA: Not applicable; RA: Rheumatoid arthritis; SpA: spondyloarthritis.

developing post-traumatic stress disorder (PTSD) could enhance the risk of developing autoimmune diseases, including RA. Based on their study of Vietnam veterans, Boscarino *et al.* [25] reported that those with RA had more PTSD symptoms compared to those without RA.

The results of those studies are in agreement with a biopsychosocial model linking psychological stress and stressful life events with the etiology of autoimmune diseases. The impact of stress, resulting from an intense life event and aggravated by conditions like emotional repression, would increase vulnerability to autoimmune diseases due to dysregulated immunity [26-30] and enhanced inflammation.

Herein, no significant difference was found between CIR and non-CIR patients regarding the frequency of depression disorders, depression severity, history of prior depressive episode(s), or anxiety symptoms.

Depressive and anxiety disorders are described as the most frequent comorbidities for CIR patients. Reynier-Legarçon *et al.* [31] found that patients with autoimmune diseases (systemic lupus erythematosus, systemic scleroderma, or primary Sjögren syndrome) presented more severe depressive and anxiety symptoms than the general population. Baerwald *et al.* [32] found that depressive disorders were significantly more common in RA patients than in the general population.

Recently, Kang [33] investigated the effect of arthritis on mental health using the 12-item version of the general health survey (GHQ-12) and reported a total of three factors of GHQ-12, that is, GHQ-12A (social dysfunction and anhedonia; six items), GHQ-12B (depression and anxiety; four items), and GHQ-12C (loss of confidence; two items), suggesting that both the global mental health and dimensions of mental health are negatively affected by arthritis. We were not able to replicate those findings, probably because of a lack of statistical power. In contrast, the homogeneity of our patients, in terms of depressive and anxiety symptoms, attenuated any potential bias linked to their emotional dysregulation associated with these psychological comorbidities.

Moreover, no significant differences were found between the RA and SpA groups for the frequency of depression and depression severity. However, RA patients reported significantly more frequent prior depressive episodes than SpA patients, a finding of which has never been reported previously. Nonetheless,

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Table 4. Psychological assessments of patients with versus without BIS

Psychological parameters	With BIS (*n*=16)	Without BIS (*n*=31)	*P*-value
Depression	13 (81.3%)	25 (80.6%)	1
Depression intensity			1
Mild/moderate	11 (84.6%)	21 (84.0%)	
Severe	2 (15.4%)	4 (16.0%)	
Previous depression	14 (87.5%)	23 (74.2%)	0.457
Anxiety	16 (100%)	31 (100%)	NA
Anxiety intensity			0.252
Mild/moderate	9 (56.3%)	12 (38.7%)	
Severe	7 (43.8%)	19 (61.3%)	
Alexithymia	16 (100%)	30 (96.8%)	1
Alexithymia intensity			0.222
Mild/moderate	5 (31.3%)	15 (50%)	
Severe	11 (68.8%)	15 (50%)	
Social desirability			0.716
Mild/moderate	12 (75.0%)	25 (80.6%)	
Severe	4 (25.0%)	6 (19.4%)	
Emotional repression			0.031*
Mild/moderate	12 (75.0%)	13 (41.9%)	
Severe	4 (25.0%)	18 (58.1%)	
Conflict-management style			**0**.02*
Avoidance	9 (56.3%)	28 (90.3%)	
Intermediate	7 (43.8%)	3 (9.7%)	
Tendency to cede responsibility to others			0.541
Mild/moderate	16 (100%)	29 (93.5%)	
Severe	0 (0%)	2 (6.5%)	
Persecution complex	3 (18.8%)	11 (35.5%)	0.321
Somatic complaints			0.555
Mild/moderate	10 (62.5%)	22 (71.0%)	
Severe	6 (37.5%)	9 (29.0%)	
Psychological complaints			1
Mild/moderate	11 (68.8%)	22 (71.0%)	
Severe	5 (31.3%)	9 (29.0%)	
Emotional expressivity intensity			0.211
Mild/moderate	9 (56.3%)	23 (74.2%)	
Severe	7 (43.8%)	8 (25.8%)	
Life event 1	11 (78.6%)	18 (60.0%)	0.314
Life event 1 intensity			0.812
Mild/moderate	6 (54.4%)	9 (50.0%)	
Severe	5 (45.5%)	9 (50.0%)	
Life event 2	15 (93.8%)	29 (93.5%)	1
Life event 2 intensity			1
Mild/moderate	10 (66.7%)	20 (69.0%)	
Severe	5 (33.3%)	9 (31.0%)	
Heavy conflictual load over the last three years	14 (87.5%)	26 (83.9%)	1
Somatic escalade	7 (43.8%)	7 (22.6%)	0.182
Actual stress level			0.541
Mild/moderate	16 (100%)	28 (90.3%)	
Severe	0 (0%)	3 (9.7%)	
Professional impact			0.75
Mild/moderate	8 (53.3%)	14 (48.3%)	
Severe	7 (46.7%)	15 (51.7%)	
Manual labor	8 (50%)	20 (64.5%)	0.337
Physical activity enjoyment pre-diagnosis	7 (43.8%)	16 (51.6%)	0.609
Physical activity enjoyment post-diagnosis	3 (18.8%)	5 (16.1%)	1

Note: Data are expressed as *n* (%) and compared using the Chi-squared test or Fisher's exact test accordingly; *$P<0.05$.
Abbreviations: BIS: Biological inflammatory syndrome; NA: Not applicable.

some findings indicated that anxiety symptoms, depression, and perception of the disease impacted the physical quality of life differently for SpA and RA patients. Some authors noted that RA patients had more physical quality-of-life difficulties, while those with psoriatic arthritis and ankylosing SpA had more mental quality-of-life issues [33-36]. Hyphantis *et al*. [37] reported that SpA patients' quality of life was associated with anxiety and not depressive symptoms, which were associated with RA patients. Our results, consistent with earlier findings, suggest a link between depression and RA patients.

Together, these results suggest that CIR (RA or SpA) patients would probably benefit from emotional management from psychotherapists and antidepressants for symptomatic depressive episodes. Moreover, these symptoms can contribute to a poorer prognosis for their respective rheumatological disease [37]. Bijsterbosch *et al.* [38] demonstrated that arthrosis patients' perceptions of their disease were predictive of the functional disability and that cognitive-behavioral therapy could modify the representations of the disease and obtain a better functional result.

A biological inflammatory syndrome was significantly associated with a low disorder of emotional regulation (mild/moderate emotional repression). However, earlier studies have reported a stronger association between emotional disorders and a biological inflammatory syndrome.

Smoak *et al.* [39] found increased nuclear factor-κB activity in patients with PTSD, resulting from childhood violence, compared to healthy controls. Howren *et al.* [40] reported that patients with depression had significantly higher interleukin-1 and -6, tumor necrosis factor-α, and C-reactive protein levels. Goldsmith *et al.* [41] also observed from a meta-analysis of 68 studies, that patients with schizophrenia, bipolar disorder, or major depressive episodes had increased levels of inflammatory cytokines. In addition, depressive symptoms were more frequent in patients with autoimmune diseases and taking anti-inflammatory drugs. Gobin *et al.* [42] found that antidepressants lowered the production of inflammatory cytokines, for example, interleukins-1β and -6 and tumor necrosis factor-α.

Several monoclonal antibodies targeting relevant inflammatory pathways for the treatment of CIR were associated with neuropsychiatric adverse events, notably depression, or suicidal

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Table 5. Psychological assessments of patients with versus without articular structural involvement

Psychological parameters	With ASI (*n*=14)	Without ASI (*n*=26)	*P*-value
Depression	11 (78.6%)	20 (76.9%)	1
Depression intensity			1
Mild/moderate	9 (81.8%)	17 (85.0%)	
Severe	2 (18.2%)	3 (15.0%)	
Previous depression	14 (100%)	19 (73.1%)	0.075
Anxiety	14 (100%)	26 (100%)	1
Anxiety intensity			0.079
Mild/moderate	4 (28.6%)	15 (57.7%)	
Severe	10 (71.4%)	11 (42.3%)	
Alexithymia	14 (100%)	25 (96.2%)	1
Alexithymia intensity			0.584
Mild/moderate	6 (42.9%)	13 (52.0%)	
Severe	8 (57.1%)	12 (48.0%)	
Social desirability			0.222
Mild/moderate	13 (92.9%)	19 (73.1%)	
Severe	1 (7.1%)	7 (26.9%)	
Emotional repression			0.191
Mild/moderate	10 (71.4%)	13 (50.0%)	
Severe	4 (28.6%)	13 (50.0%)	
Conflict-management style			0.102
Avoidance	9 (64.3%)	23 (88.5%)	
Intermediate	5 (35.7%)	3 (11.5%)	
Tendency to cede responsibility to others			0.533
Mild/moderate	14 (100%)	24 (92.3%)	
Severe	0 (0%)	2 (7.7%)	
Persecution complex	5 (35.7%)	8 (30.8%)	1
Somatic complaints			0.031*
Mild/moderate	6 (42.9%)	21 (80.8%)	
Severe	8 (57.1%)	5 (19.2%)	
Psychological complaints			0.48
Mild/moderate	8 (57.1%)	19 (73.1%)	
Severe	6 (42.9%)	7 (26.9%)	
Emotional expressivity intensity			0.007*
Mild/moderate	5 (35.7%)	21 (80.8%)	
Severe	9 (64.3%)	5 (19.2%)	
Life event 1	9 (69.2%)	14 (58.3%)	0.724
Life event 1 intensity			1
Mild/moderate	5 (55.6%)	7 (50.0%)	
Severe	4 (44.4%)	7 (50.0%)	
Life event 2	12 (85.7%)	25 (96.2%)	0.276
Life event 2 intensity			1
Mild/moderate	8 (66.7%)	16 (64.0%)	
Severe	4 (33.3%)	9 (36.0%)	
Heavy conflictual load over the last three years	11 (78.6%)	23 (88.5%)	0.646
Somatic escalade	6 (42.9%)	4 (15.4%)	0.123
Actual stress level			0.539
Mild/moderate	14 (100%)	23 (88.5%)	
Severe147	0 (0%)	3 (11.5%)	
Professional impact			0.009*
Mild/moderate	11 (84.6%)	10 (40.0%)	
Severe	2 (15.4%)	15 (60.0%)	
Manual labor	7 (50%)	15 (57.7%)	0.641
Physical activity enjoyment pre-diagnosis	3 (21.4%)	15 (57.7%)	0.028*
Physical activity enjoyment post-diagnosis	2 (14.3%)	4 (15.4%)	1

Note: Data are expressed as *n* (%) and compared using the Chi-squared test or Fisher's exact test accordingly; *$P<0.05$.
Abbreviations: ASI: Articular structural involvement; NA: Not applicable.

ideation or behavior [43]. The development of brodalumab, a molecule targeting interleukin-17, was stopped after suicidal behaviors were observed during clinical trials [44,45].

Our results, consistent with the previous studies, suggested a bidirectional relationship between depressive syndrome and biological inflammatory syndrome, but this finding should be validated in a longitudinal study. It remains to be determined whether systemic inflammation could induce emotional symptoms through neuronal cells or whether these emotional disorders are considered biological inflammatory syndrome that subsequently trigger the onset of CIR.

One of the main limitations of this preliminary study was the lack of statistical power due to a small sample size. However, this pilot study investigated potential associations between CIR and biopsychosocial factors, and its findings are indicative of areas that should be examined in greater depth in future studies. In addition, because this was an observational study, no conclusions could be drawn about any association with causality. As this was a cross-sectional investigation, it was not possible to determine whether the primary emotional regulation disorders, possibly contributing to the rheumatological disease onset or secondary disorders, should be interpreted as adaptive or coping modalities to handle a functional handicap or limiting pain caused by the disease. Our study suffered from two selection biases: (i) it was a monocentric study recruiting patients at a university hospital, representing a particular sociodemographic status; and (ii) most patients were assessed in a day for severe pathologies and comorbidities. Furthermore, the clinical psychological parameters chosen for assessment, although not subjected to consensual agreement, corresponded to clinical entities. Nonetheless, participants in this study benefited from combined psychiatric and rheumatological assessments during a day of hospitalization, which is considered novel, enabling the evaluation of a large number of psychological factors and comparing them to concomitant rheumatological findings.

5. Conclusion

Our study established an association between emotional repression, intense life events, and the etiology and development

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of CIR. Moreover, RA patients had significantly more depressive episodes than SpA patients. Our observations suggested that targeted psychotherapy could complement the clinical management of CIR.

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Conflict of Interest

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

All patients were informed about the study's objectives and agreed to the anonymous use of the collected data. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Department of Clinical Research and Innovation of the Amiens-Picardie University Hospital. The authors have obtained the written and signed informed consent of the participants before their participation.

Consent for Publication

The authors have obtained the written and signed informed consent of the patients for releasing their data in this paper.

Availability of Data

Data are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Chances and challenges of combined antegrade and retrograde endoscopic recanalization of complete hypopharyngoesophageal obliteration: a case series

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Abstract

Background: Complete hypopharyngeal obliteration is a serious problem after radiochemotherapy. Data on rendezvous techniques using percutaneous retrograde endoscopy through the gastrostomy channel and antegrade laryngoscopy are limited with a possible bias on positive results.
Aim: This study aimed to review the clinical success, challenges, complications, and failure rates of this technique.
Methods: We prospectively collected data on endoscopic recanalization techniques, subsequent bougienages, adverse events, and final outcomes in seven patients.
Results: Recanalization was technically successful in all patients. However, normal food intake was achieved in only two patients, with one of them under ongoing bougienage. Additive treatment was needed in all patients, including microsurgical scar excision, temporary stent application, argon plasma coagulation, and surgical fistula closure. Salvage laryngopharyngectomy had to be performed in two of the seven patients. Preexisting hypopharyngo-tracheal fistula and therapy-induced fistula represent a technically demanding obstacle, necessitating endoscopic stenting and surgical closure.
Conclusion: Endoscopic recanalization of esophageal obliterations is feasible, although technically demanding. The clinical success rate for long-term normalization of oral food intake is, however, low. Prospective data collection in a larger cohort is urgently needed.
Relevance for Patients: Patients should be informed about the possibility of long-term follow-up treatments and the low clinical success rate of endoscopic recanalization by the rendezvous technique, as well as other alternative approaches while making the decision to accept the treatment.

1. Introduction

Hypopharyngoesophageal strictures occur in approximately 3% of patients after radiotherapy for head and neck cancers, squamous cell carcinomas of the upper esophagus, and laryngeal or oropharyngeal cancers [1,2]. A radiation dose >45 – 60 Gy is a risk factor for stricture formation [1,3]. Complete esophageal obliteration has been reported in 23 – 50% of preselected patients with radiation-induced esophageal strictures [2,4]. The most common site for radiation-induced stenosis is the post-cricoid or cricopharyngeal region [5]. In contrast to subtotal esophageal stenosis, which can be easily treated by endoscopic bougienage, complete obstruction of the lumen usually requires alternative approaches, such as surgical revision, which is a complex and difficult procedure in the pretreated proximal esophagus [3,6].

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Although some authors advocate surgical reconstruction for complete esophageal obstruction [3,7], peroral and transgastric-retrograde rendezvous has been reported for recanalization of subtotal [8-11] and complete esophageal obstruction in single cases and case series [5,11-19] with a high technical and clinical success rate. However, a positive publication bias should be considered when assessing this technique. Patients with cancers of the hypopharynx are at considerable risk for secondary malignancies of the esophagus [20]. Therefore, re-establishment of the pharyngoesophageal passage will not only allow swallowing of saliva or even restore oral nourishment to improve the quality of life but will also enable endoscopic surveillance in these patients.

Here, we report a case series of seven technically successful recanalizations of complete pharyngoesophageal obstruction after radiotherapy by a transgastric-retrograde approach under transillumination, fluoroscopic, and endoscopic guidance.

2. Methods

2.1. Patients

Seven patients eligible for the combined antegrade and retrograde recanalization treatment presented with complete esophageal obliteration, which was confirmed by upper endoscopy. All patients gave their written informed consent for the treatment and the publication of their data.

2.2. Procedures

For recanalization of the upper esophageal entry, we performed a rendezvous technique: after percutaneous endoscopic gastrostomy (PEG) removal, the PEG channel was dilated to 8 mm (CRE PRO Wireguided Balloon Dilatation Catheter, Boston Scientific, Cork, Ireland), and a slim gastroscope (GIF XP160, 5.9 mm, Olympus, Hamburg, Germany) was propagated into the stomach and retrograded into the esophagus up to the distal end of the obliteration. Simultaneous transoral endoscopy under fluoroscopy allowed us to measure the length of the obliteration. After endoscopy, the gastrostomy was kept open by a G-tube (Nutricia Flocare Gastrostomy tube, 14 Ch). On the following day (in some cases within the same procedure), antegrade rigid pharyngoscopy and simultaneous retrograde esophagoscopy through the PEG channel were performed under general anesthesia. Under fluoroscopic, transillumination, and retrograde endoscopic guidance, the proximal blind end of the esophagus was punctured from the hypopharynx with a 1.9 mm straightened needle (Provox Vega Puncture Set, Atos Medical GmbH, Troisdorf, Germany) or with the trocar needle of the PEG set in the following cases after cutting the butterfly flanks to allow passage through the pharyngoscope (Freka PEG Set Gastric FR15, Fresenius Kabi AG, Bad Homburg, Germany). A guidewire was advanced through the needle into the esophagus and grasped with forceps via the gastroscope. The obliteration was reopened either with an endoscopic ring cutter (ring knife model Prof. Dr. U. Will, 1.8 mm, MTW, Wesel, Germany) or a biliary dilation catheter (Cook Medical, Ireland) under intravenous antibiotic coverage with clindamycin or cefuroxime in combination with metronidazole. Subsequently, the opened channel was dilated (2 – 9 mm), and a nasogastric feeding tube was inserted to guide further bougienages.

2.3. Data collection

Data concerning oncological pretreatment, duration, and symptoms of esophageal obliteration were retrospectively collected from the patient´s file. Data on clinical symptoms at presentation, diagnostic work-up, recanalization procedure, bougienage treatments, complications, symptom development, and final outcomes were prospectively collected during each visit.

3. Results

The clinical background of patients with oncologic details and demographic data are listed in detail in Table 1. The mean and median age was 64 and 70 years, respectively. Most patients (71%) were male. All but one patient received radiochemotherapy for their initial oncological treatment. In all patients, a complete esophageal obliteration occurred with complete aphagia, which was verified by a computed tomography scan, lack of contrast media passage, and upper endoscopy. The mean and median length of obliteration was 16.8 and 20 mm, respectively. Details of the recanalization procedure are given in Table 2, and the standard procedure is depicted in Figure 1. The technical success rate of the recanalization procedure in all seven patients was 100%.

Periprocedural complications occurred in only one patient where the preparation needle induced the formation of a 15 mm wide soft-tissue pocket of the esophageal lumen adjacent to the left common carotid artery (Figure 2). To facilitate 6 weeks of pocket obturation by granulation, weekly bougienages under antibiotic coverage were carried out only up to 9 mm, and secretion drainage was ensured by wire-guided insertion of a small gastric tube after each bougienage.

After successful recanalization of the obliterated passage, an average of 30.9 (range 12 – 97) bouginages and balloon dilatations were performed on a weekly or biweekly basis to a final mean diameter of 15.3 mm (range 10 – 20 mm). Additive treatment during bouginage was necessary in six of the seven patients (86%); two patients (#1, #5) needed temporary metal stent implantation (fcSEMS) for fistula with final surgical fistula closure (Figure 3A). Due to the COVID-19-induced restrictions of medical care, one patient (#3) omitted routine follow-up, developed another esophageal occlusion, and needed a second recanalization procedure. Three patients (#4, #6, #7) underwent microsurgical scar excision to improve the entry into the recanalized segment (Figure 3B). Three patients (#1, #4, #5) were treated with argon plasma coagulation for enhanced scar formation and granulation tissue in addition to local triamcinolone treatment (Figure 3C).

After the treatment, all patients could at least consume semisolid food and swallow saliva. Two patients (#3, #5, 29%) resumed normal foot intake and remained PEG-independent, with one of them needing ongoing bougienage. Patient #3 was still under repeated bi- to tri-weekly bouginage, while the other patient (#5) had been healthy, reporting no other complications and needing

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Table 1. Patients' characteristics

Parameter	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7
Age (years)	73	70	72	31	59	67	74
Sex	Male	Male	Female	Female	Male	Male	Male
Tumor (histopathology)	Oropharyngeal carcinoma and synchronous supraglottic carcinoma of the larynx (squamous cell carcinoma)	Oropharyngeal carcinoma (squamous cell carcinoma)	Hypopharyngeal carcinoma (squamous cell carcinoma)	Hypopharyngeal carcinoma (squamous cell carcinoma)	Supraglottic carcinoma of the larynx (squamous cell carcinoma)	Glottic carcinoma of the larynx	Carcinoma of the larynx (squamous cell carcinoma)
TNM (UICC)	pT2 pN2c cM0 R1 pT2 pN2a cM0 R0	cT4 cN0 cM0	cT2 cN0 cM0	cT4 cN2b cM0	pT3 pN3b M0	cT3 cN0 cM0	cT3 cN0 cM0
Oncological treatment modalities	Total laryngectomy and partial resection of oropharynx, reconstruction, aRCHT	pRCHT	pRCHT	ICT + pRCHT	Total laryngectomy with neck dissection	Tumor debulking, pRCHT	pRCHT
Additional neoplasia	NCSLC*, pT4 cN2 cM0 (RCHT 45Gy) Skin cancer (squamous cell carcinoma, head/neck) pT1 pNx R0	Prostate cancer, pT3 pN0 R1 (radical prostate resection) Squamous cell cancer esophagus* 20 cm from incisors (RCHT)	NCSLC, cT2 cN2 cM0, synchronic (RCHT)	None	None.	None	None

Abbreviations: NCSLC: Non-small cell lung cancer; RCHT: Radiochemotherapy; TNM: Staging according to T=Primary tumor, N=Lymph node metastases, and M=Distant metastases. UICC: Union International Contre le Cancer (International Union against Cancer).

Table 2. Synopsis of treatment

Parameter	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7
Length of obliteration (mm)	20	8	20	30	5	30	5
Means of recanalization	Ring cutter, ERC-Balloon 7 mm, bougienage 7 mm	Ring cutter, bougienage 5 mm	ERC Dilatator (7F), bougienage 9 mm	ERC Dilatator (10F), bougienage 5 mm	Ring cutter, bougienage 5 mm	EUS cystotome (10F), bouginage 7 mm	ERC Dilatator (6F), bouginage 5 mm
Technical success of recanalization	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number of bougienages/ balloon dilatations	8/5	18/4	12	50/47	28/11	17/4	7/5
Final diameter (mm)	10	18	15	16	12	16	20
Additional measures	Three fcSEMSs, surgical fistula closure, APC	RCHT for secondary tumor	Reopening due to re-occlusion	Microsurgical scar excision, triamcinolone, APC	fcSEMS, APC, surgical fistula closure, triamcinolone	Microsurgical scar excision	Microsurgical scar excision
Final outcome	Deceased 3 month after last fcSEMS implantation	Laryngectomy rejected by patient, palliative care for osteolytic infection	Normal eating, PEG removed	Salvage laryngopharyngectomy for esophago- tracheal fistula	Bougienage ongoing, PEG-independent	Bougienage ongoing, PEG-dependent	Salvage laryngopharyngectomy

Abbreviations: APC: Argon plasma coagulation; fcSEMS: fully covered self-expanding metal stent; PEG: Percutaneous endoscopic gastrostomy; RCHT: Radiochemotherapy.

no other treatments, for 958 days after her last bougienage. One patient died shortly after recanalization from lung cancer (#1). One patient (#2) was treated with definitive radiochemotherapy for a secondary poorly differentiated esophageal squamous cell cancer, detected 495 days after recanalization. Externally performed radiotherapy overlapped with the initial radiation field, resulting in esophageal wall necrosis with osteomyelitis and spinal metal implantation (Figure 4A). The patient was lost

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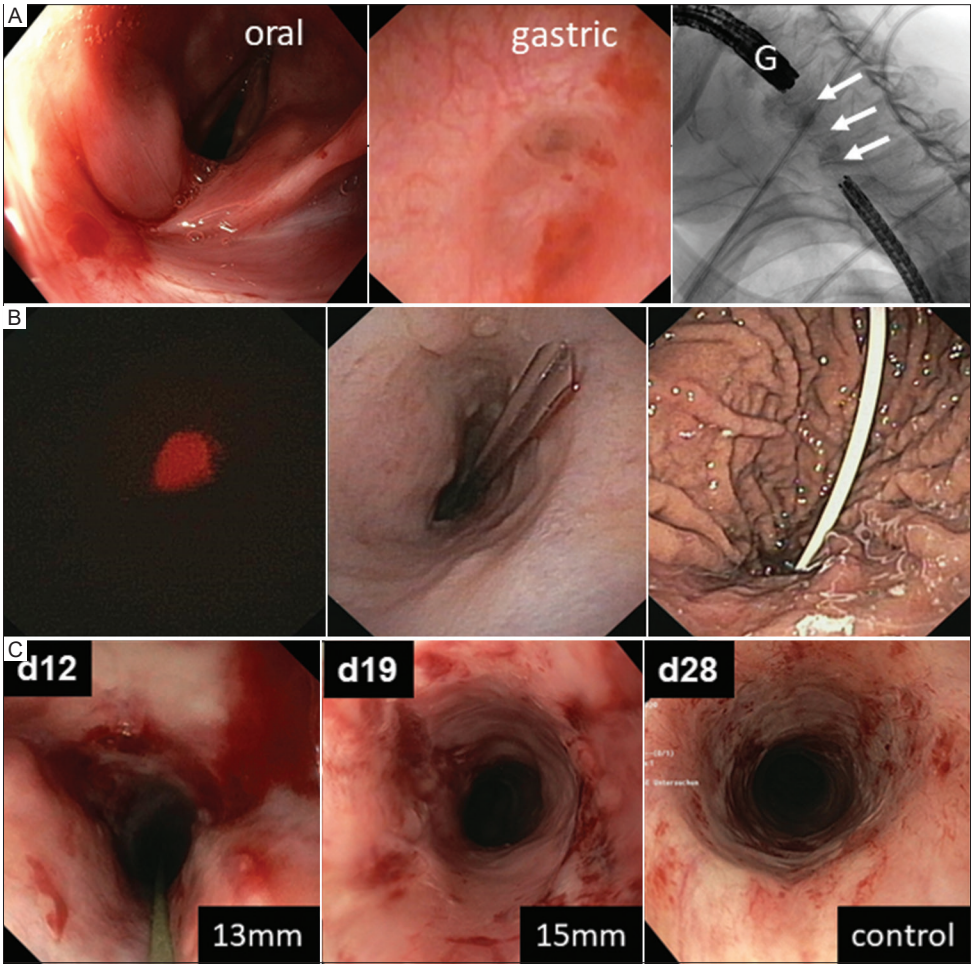

Figure 1. Transgastric-retrograde rendezvous for recanalization of complete esophageal obstruction. (A) Normal gastroscope passage from the oral side was blocked by a complete esophageal obstruction (left). Retrograde esophagoscopy via the percutaneous endoscopic gastrostomy (PEG) channel showed complete obstruction from the gastric side (middle). Simultaneous ante- and retro-grade endoscopy via gastrostomy revealed a 20 mm esophageal occlusion (right, white arrows). (B) Periprocedural transillumination from the antegrade pharyngoscope was detected by retrograde endoscopy via the PEG channel (left). The middle picture shows the per-oral puncture in rendezvous technique and the right picture shows the insertion of a duodenal feeding tube after recanalization of the esophagus. (C) Repeated bougienages at the indicated time points led to a diameter of up to 15 mm.

to follow-up in this palliative setting. Two patients needed salvage laryngopharyngectomy operations: One (#7) decided in favor of an operation after 12 dilatation sessions failed to bring clinical improvement. Another patient (#4) developed a therapy-induced esophago-tracheal fistula (F - fistula, E - esophagus, Figure 4B) and failed to achieve therapeutic success after a long-term bouginage of 97 treatment sessions.

4. Discussion

Recanalization of obliterated esophageal stenosis is a complex multidisciplinary procedure and requires unconventional and individualized solutions to a multitude of problems and complications. Compared with combined ante- and retro-grade recanalization, antegrade endoscopic recanalization results in less complications but involves a longer intervention time [21]. Nevertheless, we are concerned that the previously reported positive clinical results of the procedure might be overstated due to a positive publication bias.

The reported median length of reopened obliterations was 23 mm with a wide range of 2 – 55 mm [18]. The reported primary technical success rates for recanalization of complete obliterations were high: 18/19 patients [18], 5/6 patients [22], 5/5 patients [13], 7/8 patients [19], and 11/11 patients (with 21 procedures) [21]. In our series, all obliterations were successfully recanalized.

There is a high variability in the used techniques and material in our series as well as in published cases. For puncture of the obliterated tissue, endosonography needles have been reported to be challenging due to their high flexibility [13], but have been successfully applied by others [18]. We attempted applying an ultrasound needle (19G, Olympus EZ Shot) in only one patient, but the tractability of the needle was too high for successful puncture, possibly resulting in a pocket formation

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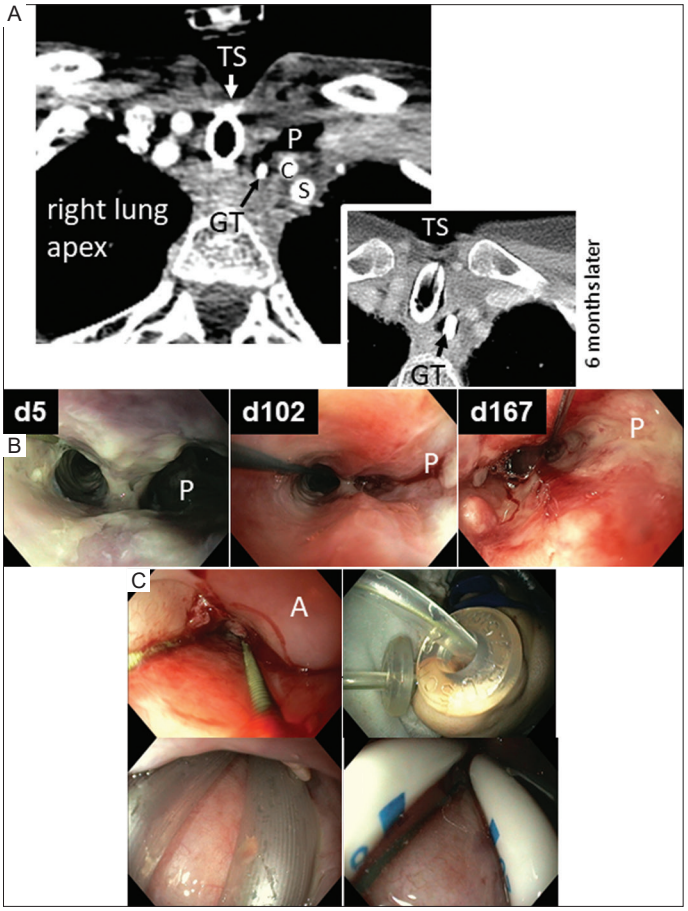

Figure 2. Periprocedural complications. (A) Axial computed tomography plane of the upper thorax aperture demonstrates the soft tissue pocket (P) at the plane of the tracheostomy (TS) adjacent to the common carotid artery (C), left subclavian artery (S) and left lung. The gastric tube (GT) was placed as a placeholder in the esophageal lumen. The inset is an image showing the condition after tissue pocket healing 5 months later. (B) The time-consuming healing of the tissue pocket (P) delayed the progress of bougienages by approximately 100 days. (C) To keep the dilated esophageal entrance next to the arytenoid cartilage (A) open until subsequent bougienage, two guidewires for two gastric tubes were inserted (upper left). Wire-guided and simultaneous insertion of the two gastric tubes had to be assisted by Wendl tubes, one in each nostril (upper right), which splinted the pharynx (lower left) and enabled the simultaneous insertion of two gastric tubes (lower right).

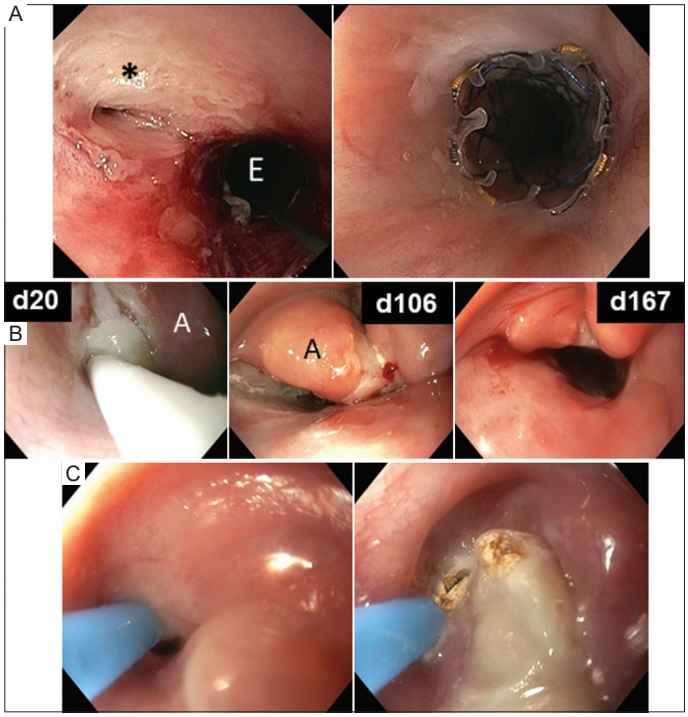

Figure 3. Additive treatments during bouginage. (A) After the eighth bougienage of the recanalized esophagus (E), an esophago-tracheal fistula became evident in patient #1 (*, left) and was endoscopically closed by a fully covered 10 × 100 mm biliary stent (right). (B) To widen the entrance into the recanalization below the arytenoid cartilage, scar tissue was removed by repeated microsurgery, thereby shifting the entrance to the middle (patient #4). (C) Due to recurrent scar formation and granulation tissue cytoreductive, argon plasma coagulation therapy was applied in patient #7.

due to repeated maneuvers with the endosonography needle (patient #4). Needle knife preparation [18] and puncture with the hard end of a wire [22], as well as puncture with a trocar needle from the pharyngeal side [14], as in our cases, have also been reported. Using a stiff needle for puncture from the pharyngeal site offers some advantages regarding maneuverability, especially in obliterations over a longer distance, but still harbors the risk of injuring adjacent and vulnerable structures. Blunt preparation from the oral side under fluoroscopic and endoscopic guidance and puncture of the remaining short segmented soft tissue might be preferable in short-distance occlusions.

Insertion of a feeding tube until repeated bougienages [18] or even the temporal placement of a small-diameter covered metal stent (≤10 mm) [13,14] has been reported as approaches to keeping the pharyngoesophageal passage open after recanalization. However, immediate metal stent insertion did not seem to reduce the necessity of subsequent and repeated bougienages but was associated with a higher abscess formation rate [13]. In this case series, fully covered self-expanding metal stents (fcSEMSs) were used only when fistulas coexisted with the recanalized pharyngoesophageal channel and they did not reduce the need for repeated bougienage. From our experience, the insertion of a gastric tube as a placeholder is highly recommended until the lumen is stable enough to prevent reocclusion. To maintain a functional passage, patients needed up to 32 [18] or even 37 bougienages [4]. In this case series, up to 97 treatment sessions were performed on one patient who did not agree to salvage operation.

An overall complication rate of 11% was reported in the literature for the applied rendezvous technique [15]. It has been reported that mediastinal emphysema [22], pneumothorax [12], pneumomediastinum with periesophageal abscess formation and cervical osteomyelitis, cervical abscess formation [13], and microperforation [19] are mainly managed conservative mode. In

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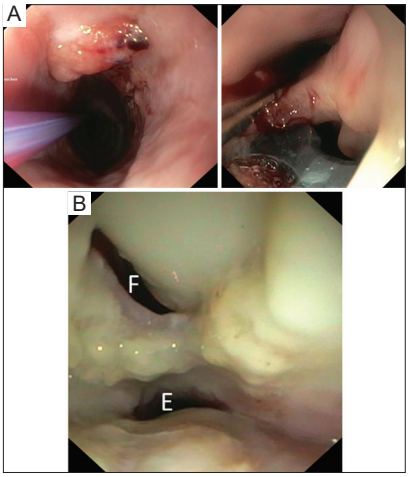

Figure 4. Final outcome. (A) Endoscopic images showing secondary squamous cell carcinoma 3.5 years after initial definitive radiochemotherapy of an oropharyngeal cancer, detected 495 days after recanalization of pharyngo-esophageal obliteration. Radiotherapy resulted in esophageal wall necrosis with an open view of the spine after metal implantation. (B) After 97 bouginages and balloon dilatations, patient #4 developed a therapy-induced esophago-tracheal fistula (F - fistula, E - esophagus).

the seven cases reported in this series, only one direct complication of the recanalization occurred but was managed conservatively.

Despite a high initial technical success rate, the clinical success rate was quite low with a high percentage of additive invasive measures and salvage operations. Although only a minority of reported cases had achieved euphagia without further symptoms (2/19, [18]; 6/24 [15]), most patients could at least consume semisolid food (11/19, [18]; 19/25, [4]; 11/25, [15]) or reported an improvement of their dysphagia score [11]. A recent meta-analysis of 19 studies showed a technical success rate of 89%, but a PEG-free improvement of dysphagia in only 58% [23]. In our cohort, this rate was even lower, measuring only 14%.

Additional adhesions in the hypopharynx and larynx, pronounced scar formation and propulsive dysfunction hamper a normal act of swallowing even after successful treatment of esophageal strictures [24], and approximately 20% – 60% of patients are still dependent on their PEG after recanalization [4,5,15,18,22]. Advanced laryngeal scar formation might hamper the well-coordinated act of swallowing after recanalization. Concomitant intensive swallowing training is essential for clinical success. In addition, in 43% of our patients, microsurgery with scar remodeling was necessary to restore the best possible anatomy to facilitate food passage into the recanalized esophageal entrance. Argon plasma coagulation had been applied in some cases to reduce excessive scars but might have contributed to the esophagotracheal fistula which formed after 97 bouginages in patient #4, resulting in salvage laryngopharyngectomy. Therefore, ablative techniques must be applied with utmost caution.

Tumor surveillance is an important management aspect for hypopharyngeal cancer patients, as they often harbor risk factors for other malignancies [20,25,26]. In one recent case report, localized synchronous squamous cell carcinomas of the esophagus 22 cm from the incisors and hypopharynx were treated by definitive chemoradiotherapy [27]. Definitive radiochemotherapy in our patient was, however, complicated by impaired wound healing, esophageal necrosis, fistula formation, and osteomyelitis.

This study has several limitations. Despite the prospectively collected data, we had no well-defined criteria for which techniques and material to be used, for the time intervals of bougienage and the additive treatments. Long-term follow-up data are needed to demonstrate a long-term benefit even in the two patients with the best result reported in this series. Due to the rarity of this treatment modality, we were only able to provide data on a very small cohort. We propose to prospectively collect data in a multicenter study designed with a predefined instrumental armamentarium, treatment intervals, and outcome parameters.

Applying alternative endoscopic techniques like the per-oral endoscopic tunneling for recanalization of completely obliterated esophageal obstructions has been reported in literature [28-30]. Although this technique holds huge potential, it is very technically demanding, and more investigations are warranted to validate its technical and clinical superiority over the rendezvous procedure.

5. Conclusion

Reestablishment of the pharyngoesophageal passage in patients with complete obstruction after radiochemotherapy can be achieved by a rendezvous technique of antegrade pharyngoscopy and transgastric-retrograde esophagoscopy. However, these patients require highly individualized treatment and follow-up with the need for interdisciplinary, unconventional, and sometimes highly experimental approaches to manage post-interventional obstacles. Despite successful recanalization, complete normalization of the complex act of swallowing can only be expected in a small percentage of patients, and many patients might need repeated interventions over many years. Thus, before implementing the procedure, patients should be informed of the possibility of long-term follow-up interventions. To avoid reocclusion and secondary malignancies, strict and continuous follow-up must be arranged for these patients.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

Conceptualization: Ronald Koschny, Gerhard Dyckhoff
Data acquisition/clinical care: All authors
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Ethics Approval and Consent to Participate

Since patient treatment was performed in the context of routine clinical care, prior ethics application was not obtained.

Consent for Publication

Informed consent was obtained from each patient to publish their data anonymously.

Availability of Data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Analysis of the effects of pulsed microcurrent on pain, depression, and anxiety in patients with herpes zoster

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Abstract

Background: Herpes zoster is a common viral skin infection and has a high incidence rate in China. At present, conventional drugs combined with adjuvant measures are used for treatment. To improve the efficiency and shorten the time of treatment, we propose the use of pulsed microcurrent as a new adjuvant therapy.
Aim: This study aimed to investigate the effects of pulsed microcurrent on pain, depression, and anxiety in patients with herpes zoster.
Methods: A total of 58 patients with herpes zoster who were admitted to our hospital between April and August 2022 were selected as study participants and divided into two groups. The control group (n = 29) received conventional drug therapy, while the experimental group (n = 29) received pulsed microcurrent electrical therapy in combination with conventional drug therapy.
Results: After 14 days of treatment, the scores from the visual analog scale, patient health questionnaire (PHQ) (i.e., PHQ-9), and generalized anxiety disorder (GAD) assessment (i.e., GAD-7) of the experimental group were reportedly significantly lower than those the control group ($P < 0.05$).
Conclusion: These findings suggested that pulsed microcurrent electrical therapy combined with conventional drug therapy could effectively alleviate the pain, depression, and anxiety symptoms in patients with herpes zoster, highlighting its potential to be widely used in clinical practice.
Relevance for Patients: Patients suffering from herpes zoster may opt for pulsed microcurrent electrical therapy to effectively alleviate the pain, depression, and anxiety symptoms.

1. Introduction

Herpes zoster is a viral skin infection that manifests in immunocompromised individuals and is caused by the varicella-zoster virus in the trigeminal ganglion. The condition is characterized by severe pain and herpetic lesions, significantly impacting an individual's quality of life and often triggering depression and anxiety [1]. The current guidelines for diagnosis and treatment [2] recommend conventional therapeutic approaches for herpes zoster, inclusive of antiviral agents combined with neurotrophic support, anti-inflammatory drugs, analgesics, and potential adjunctive physiotherapy in China [3]. While pulsed radiofrequency technology has been extensively studied for postherpetic neuralgia, the approach is challenged by the long duration of treatment, specific puncture positioning techniques, and cumbersome standardization of radiofrequency parameters [4-8]. Consequently, therapeutic outcomes of pulsed radiofrequency technology remain suboptimal. A pulsed microcurrent electrical neuromuscular stimulator (Figure 1) is a portable and wearable device that is commercially available and can function as an adjunctive treatment option.

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Figure 1. A pulse microcurrent electrical neuromuscular stimulator.

The device mechanism is relatively similar to transcutaneous electrical nerve stimulation and additionally induces analgesic effects, similar to pulsed radiofrequency therapy [9]. Herein, this study aimed to investigate the effect of pulsed microcurrent on pain, depression, and anxiety experienced by patients with herpes zoster, thereby suggesting a new adjunctive therapeutic option for herpes zoster.

2. Methods

2.1. Study design and population

The cohort study of herpes zoster in China (i.e., the COMFORT study) is an ongoing single-center, prospective, observational study that started in April 2022 to investigate the effects of pulsed microcurrent on pain, depression, and anxiety of herpes zoster patients in China. This study was approved by the Human Research Ethics Committee of the First Affiliated Hospital of Xi'an Medical University.

2.1.1. Inclusion criteria

The inclusion criteria for this study were established based on the Chinese expert consensus on herpes zoster [2], and the criteria are as follows: (i) Adult patients aged 18 years and older; (ii) patients diagnosed with herpes zoster; (iii) patients who had not received anti-varicella zoster virus treatment after the onset of the infection (e.g., antiviral drugs, analgesics, and nerve protectors); (iv) patients with pain intensity of the ≥3 points on the visual analog scale (VAS) (reported within 7 days from the onset of herpes zoster); (v) patients who voluntarily received the relevant assessments (i.e., VAS, nine-item patient health questionnaire [PHQ-9], and seven-item generalized anxiety disorder assessment [GAD-7]); and (vi) patients who provided informed consent and were compliant to the treatment regimen.

2.1.2. Exclusion criteria

The exclusion criteria for this study were: (i) Patients with specific herpes zoster conditions, such as ophthalmic or internal organ involvement; (ii) patients with severe systemic diseases or organ dysfunction; (iii) patients with a history of allergy or hypersensitivity to pulsed microcurrent or conventional therapeutic medications; (iv) patients with psychiatric diseases or cognitive dysfunction that impairs normal verbal communication; or (v) patients deemed unsuitable for participation in this study by the judgment of the researcher, such as some patients who had poor compliance and low cognition.

2.2. Patient groups

The included patients were divided into the experimental and control groups according to a random allocation table generated using the Statistical Analysis System software.

2.2.1. Control group

The conventional medication regimen of the control group comprised: (i) Valaciclovir hydrochloride capsules, taken orally, 0.6 g/dose, three times daily; (ii) methylcobalamin tablets, taken orally, 0.5 mg/dose, three times daily; (iii) vitamin B_1 tablets, taken orally, 10 mg/dose, three times daily; (iv) fusidate cream, topically administered to the affected area, twice daily (or as required by the patients based on their condition); (v) prednisone acetate tablets, taken orally, once daily, administered after 6 AM, at the following dosages for a total of 7 days (5 mg/dose): days 1 and 2: 80 mg/day; days 3 – 4: 30 mg/day; days 5 and 6: 15 mg/day; and day 7: 5 mg/day; (vi) glycolite lotion, topically administered to the affected area, twice daily; (vii) aminophenol dihydrocodeine tablets, taken orally, 1 – 2 tablets every 4 – 6 h or as needed by the patients for pain relief (up to a maximum of 8 tablets/day).

2.2.2. Experimental group

The experimental group received pulsed microcurrent electrical therapy in combination with conventional drug therapy. The pulse microcurrent electrical neuromuscular stimulator (model ICW-001, Xi'an Aikaier Medical Technology Co., Ltd., China) consisted of a wristwatch-style main unit and electrode pads, equipped with intensity adjusters (mid-frequency: 1 – 30 kHz; low-frequency: 1 – 120 Hz), auditory feedback, and a pulse width range of 30 μs to 30 ms. Treatment procedures were carried out in accordance with the provided instructions, with patients wearing 4 – 8 electrode pads daily based on their physical condition. Each session of electrode pad application lasted for 4 – 8 h/day.

2.3. Assessments

2.3.1. VAS

VAS is a linear horizontal 10 cm scale, where the ends are labeled "no pain" and "most severe pain imaginable." After pulsed microcurrent stimulation, the patients were to draw a vertical line on

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the scale within 30 s to indicate the pain intensity, which was rated from 0 to 10: 0: No pain; 1 – 3: Mild/moderate pain; 4 – 6: Severe pain; 7 – 10: Very severe pain/most severe pain imaginable [10].

2.3.2. PHQ

PHQ-9 was used to assess symptoms of depression and measure the response to treatment. Each item was rated on a four-point scale, and the responses were summed to provide a total score ranging from 0 to 27, with higher scores indicating a greater frequency of symptoms [11,12].

2.3.3. GAD assessment

GAD-7 was used to measure symptoms of generalized anxiety before treatment and 2 weeks after treatment [13]. The items were graded based on the Likert scale (i.e., 0: not at all; 1: several days; 2: more than half the days; and 3: nearly every day), where the total scores could range from 0 to 21. We used the Chinese version of the GAD-7, which was validated in a previous study [14]. In this study, patients completed the GAD-7 within a short time (approximately 3 min).

2.4. Observational analysis

The levels of pain, anxiety, and depression of the patients in both groups were assessed before and after treatment (i.e., after 14 days). To evaluate the efficacy of pain management, the reduction rate (RR) of the treatment was calculated as follows [15]:

RR = (Pre-treatment score – post-treatment score)/Pre-treatment score × 100% (I)

The criteria for evaluating the efficacy of pain management were as follows: (i) Cured: symptoms disappeared or substantially disappeared, with RR exceeding 75%; (ii) significant effect: noticeable improvement in symptoms, with RR ranging from 50% to 75%; (iii) effective: symptoms improved, with RR between 25% and 50%; (iv) ineffective: no significant improvement in symptoms, with RR equal to or less than 25%. The total effective rate was calculated using the formula:

Total effective rate = (Number of cured cases + number of significant effect cases + number of effective cases)/total number of cases × 100% (II)

In both patient groups, the severity of depression and anxiety was evaluated using PHQ-9 and GAD-7, respectively, before and after treatment. Higher scores on both scales corresponded to a greater degree of depression and anxiety, respectively.

2.5. Statistical analysis

Statistical analysis was conducted using SPSS 22.0 (IBM, USA). Descriptive statistics for the measurement data are presented as mean ± standard deviation. The comparison between groups was performed using the independent samples *t*-test. Within-group comparisons were assessed using either the rank-sum test or paired samples *t*-test. The Chi-squared (χ^2) test was employed for the analysis of count data. Statistical significance was determined at a significance level of $P < 0.05$.

3. Results

3.1. Sample characteristics

A total of 58 patients diagnosed with herpes zoster were recruited from the outpatient dermatology department of the First Affiliated Hospital of Xi'an Medical College between April and August 2022. The patients were divided into two groups: 29 patients in the experimental group and 29 patients in the control group. Within the experimental group, there were 16 male and 13 female patients with an average age of 52.47 ± 3.28 years, ranging from 35 to 68 years. In general, the duration from herpes zoster onset was 14–21 days [16], while the average duration of this study was 11.35 ± 2.78 days. The control group consisted of 15 male and 14 female patients with an average age of 55.63 ± 4.96 years, ranging from 37 to 71 years. The average duration from herpes zoster onset was 15.17 ± 3.32 days, ranging from 9 to 24 days. Statistical analysis revealed that there were no significant differences in gender and age between the two groups ($P > 0.05$), ensuring their comparability. However, a statistically significant difference was observed in the duration from herpes zoster onset between the groups ($P < 0.05$).

3.2. Comparison of VAS scores of both groups before and after treatment

Before treatment, there was no statistically significant difference observed in the VAS scores between the two groups (0.1076 ± 0.1070; 95% confidence interval [CI]: (−0.1068, 0.3220); $P > 0.05$). After 14 days of treatment, a significant discrepancy in VAS scores was observed in both groups in comparison to the pre-treatment status (0.6841 ± 0.2175; 95% CI: (0.2485, 1.1198); $P < 0.05$). Moreover, the VAS scores of the experimental group were significantly lower than those of the control group ($P < 0.05$) (Table 1).

3.3. Comparison of the efficacy of pain management between the control and experimental groups

Statistical analysis of the efficacy of pain management revealed that the experimental group exhibited a significantly higher efficacy rate (96.55%) in comparison to the control group (86.21%) ($P < 0.05$) (Table 2).

3.4. Comparison of psychological states of both groups before and after treatment

After treatment, the PHQ-9 and GAD-7 scores of both groups were lower than their respective pre-treatment scores. Furthermore, the PHQ-9 scores of the experimental group were significantly

Table 1. Comparison of VAS scores of both groups before and after treatment

Condition	VAS scores	t	*P*	95% CI
Before treatment (*n*=29)	0.1076±0.1070	1.005	0.319	(−0.1068, 0.3220)
After treatment (*n*=29)	0.6841±0.2175	3.146	<0.01	(0.2485, 1.1198)

Abbreviation: CI: Confidence interval; *n*: Number of patients; *P*: *P*-value; *t*: *t*-value; VAS: Visual analog scale.

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lower than the control group (t = 9.8287; 95% CI: (2.4551, 2.8116); P < 0.001). Similarly, the GAD-7 scores of the experimental group were also significantly lower than the control (t = 7.8190; 95% CI: (3.4477, 3.7689); P < 0.001) (Table 3).

3.5. Side effects

During the study, two patients in the control group (6.90%) and one patient in the experimental group (3.45%) experienced mild nausea and vomiting. The nausea and vomiting disappeared after a few days without any therapy. After further evaluation, it was concluded that nausea and vomiting were caused by the use of valaciclovir, as these are common adverse reactions of valaciclovir. Nonetheless, none of the patients withdrew from the study because of the nausea and vomiting. There were no other adverse effects reported during the follow-up period, and the patients did not experience any discomfort or symptoms due to the use of therapeutic drugs or the pulse microcurrent electrical neuromuscular stimulator.

4. Discussion

Herpes zoster is a viral ailment associated with high morbidity, and its clinical symptoms primarily manifest as severe pain and herpes lesions. These symptoms may predispose patients to varying degrees of anxiety and depression, ultimately affecting their quality of life. Contemporary research implicated neuralgia as the primary cause of the severe pain caused by herpes zoster, primarily associated with central nerve abnormality and peripheral neuropathy induced by viral neuropathic invasion. Therefore, the treatment of herpes zoster focuses on antiviral therapy, neurotrophic support, anti-infective measures, and pain management [3]. In this study, the control group received conventional drugs recommended by the guidelines for the diagnosis and treatment of herpes zoster, while the experimental group received treatment with a pulse microcurrent electrical neuromuscular stimulator in conjunction with conventional drugs. Pulse therapy is a physical therapy modality that combines the meridian theory from traditional Chinese medicine with modern bioelectronic principles derived from acupuncture therapy. This technique leverages electrical stimulation to promote blood circulation, alleviate qi and blood stagnation, and ultimately reduce pain [17]. Certain studies have reported that appropriate, low-frequency pulsed current may activate endogenous morphine-like polymorphic neurons in the brain, thereby providing analgesic efficacy, while eliminating pain-causing chemical mediators and reducing the chemical factors of pain [18]. In addition, low-frequency pulse therapy may enhance microcirculation in the body, facilitate nerve repair, excite neuromuscular tissues, improve nutrition, expedite the absorption and dissipation of inflammatory substances, and alleviate pain from diverse causes [19]. However, low-frequency pulse therapy has not been specifically applied for the treatment of herpes zoster-associated pain.

Pulsed microcurrent stimulation involves the application of microcurrent to acupoints, employing specific frequencies, intensities, and waveforms of electric current in accordance with therapeutic needs [20]. This technique harnesses the electrical responses of nerves and muscles to low and moderate frequencies, delivering gentle electric currents across the skin surface. Furthermore, the use of electrodes stimulates targeted acupoints and exerts its therapeutic influence on the treated area, suggesting its prospective application for specific medical conditions [21].

The pulse microcurrent electrical neuromuscular stimulator utilized in this study had adjustable intensity settings for both mid-frequency (1 – 30 kHz) and low-frequency (1 – 120 Hz) ranges. As frequency and intensity correspond to each other, adjusting the intensity settings could align the frequency for specific therapeutic requirements, producing the combined effects of mid-frequency and low-frequency pulsation therapy. Our findings demonstrated that, following a 14-day treatment period, the experimental group exhibited a shorter infection duration than the control group. In addition, the experimental group displayed significantly greater improvements in pain, depression, and anxiety levels than the control group. Previous studies predominantly focused on the application of pulse radiofrequency in the physiotherapy of herpes zoster-associated pain [8,22,23] and subsequently reported remarkable efficacy. However, no reports on the utilization of pulsed microcurrent electrical therapy have been identified. Both pulse radiofrequency and pulsed microcurrent electrical therapy share similar mechanisms of action as pulse therapies. Nevertheless, pulse radiofrequency employs higher frequencies (≥300 kHz) and voltages (≥45 V), whereas the pulse microcurrent

Table 2. Comparison of the efficacy of pain management between the control and experimental groups

Group	Criteria for the efficacy of pain management (*n*)				Efficacy (%)
	Cured	Significant effect	Effective	Invalid	
Control (*n*=29)	12	8	5	4	86.21
Experimental (*n*=29)	15	10	3	1	96.55#

Note: Chi-square statistic (χ^2)=7.779, P=0.005; #P<0.05 relative to the control group.
Abbreviation: *n*: Number of patients.

Table 3. Comparison of psychological status scores of both groups before and after treatment

Assessment	Condition	Scores	*t*	*P*	95% CI
PHQ-9	Before treatment (*n*=29)	0.0335±0.1637	0.2965	0.7680	(0.0065, 0.0663)
	After treatment (*n*=29)	2.6333±0.0890*#	9.8278	<0.001	(2.4551, 2.8116)
GAD-7	Before treatment (*n*=29)	−0.3386±0.1750	0.8655	0.3904	(−0.6893, 0.0121)
	After treatment (*n*=29)	3.6083±0.0802*#	7.8190	<0.001	(3.4477, 3.7689)

Note: *P<0.05 relative to before treatment; #P<0.05 relative to the control group.
Abbreviation: CI: Confidence interval; GAD-7: Seven-item generalized anxiety disorder assessment; n: Number of patients; *P*: *P* value; PHQ-9: Nine-item patient health questionnaire; *t*: *t*-value; VAS: Visual analog scale.

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electrical neuromuscular stimulator utilizes lower frequencies and voltages (≤21 V).

It has been reported that pain severity is correlated to the impact on the quality of life of individuals suffering from herpes zoster-related pain [24]. Furthermore, the integration of the pulsed microcurrent with standard medication in the experimental group resulted in superior pain relief outcomes compared to the control group. This combined approach also effectively ameliorated depression and anxiety symptoms in the patients, consistent with the findings by Zhang *et al.* that distinct pulsed radiofrequency temperatures resulted in notable improvements in pain, depression, and anxiety among postherpetic neuralgia patients [25].

Immunosuppression, particularly prevalent among the elderly, stands out as a pivotal factor in the onset of herpes zoster. Beyond the age of 50, there is a gradual waning of varicella zoster virus-specific cell-mediated immunity, leading to an increased occurrence of herpes zoster. The prevalence of herpes zoster in China closely mirrors that of other global regions, with an incidence rate among the elderly aged 50 and above of 2.9–5.8 cases per 1000 people [26]. Notably, the present study featured a relatively small sample size with a broad age spectrum, i.e., the mean age of the experimental and control groups was 52.47 ± 3.28 and 55.63 ± 4.96 years, respectively. The experimental group, characterized by a comparatively younger average age, exhibited a significantly shorter recovery duration than the control group, suggesting a potential synergistic effect of age and pulsed microcurrent electrical therapy.

5. Conclusion

Pulsed microcurrent electrical therapy demonstrated remarkable effectiveness in reducing herpes zoster-related pain. Consequently, the intervention also significantly alleviated herpes-zoster-induced depression and anxiety in patients. Taken together, the widespread implementation and utilization of pulsed microcurrent electrical therapy in clinical settings hold significant promise as a therapeutic option for herpes zoster. However, further studies are warranted to delve into the underlying mechanisms involved in the reduction of herpes zoster-associated pain.

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Conflicts of Interest

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

This study was approved by the Human Research Ethics Committee of the First Affiliated Hospital of Xi'an Medical University.

Consent for Publication

The authors have obtained the written and signed informed consent of the patients for releasing their data in this paper.

Availability of Data

Data are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Utilizing radiomic features of arterial phase computed tomography for delineating parathyroid adenomas from surrounding anatomical structures

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ABSTRACT

Aim: The study aimed to correlate radiomic data of four-dimensional computed tomography (4D-CT) with pathology-proven parathyroid adenomas to identify and quantitate select dimensional and textural features that predict parathyroid adenomas with a high degree of confidence, with the ultimate goal of improving the reliability of parathyroid adenoma detection so as to facilitate the subsequent unilateral minimally invasive parathyroidectomy (MIP).

Methods: A total of 144 subjects with a history of neck 4D-CT, parathyroidectomy, and intraoperative pathology-proven parathyroid adenoma(s) were retrospectively reviewed. Following the exclusion of patients with a thyroidectomy, unsuccessful surgery, or indeterminate localization of the parathyroid adenoma on 4D-CT, a preliminary sample of 20 patients was obtained. Four anatomical structures (carotid artery, internal jugular vein, thyroid, and parathyroid adenoma) were segmented twice on 25-second arterial phase axial sections of a 4D-CT, and radiomic data of the shape, first-order, and second-order classes (106 variables) were extracted from the four structures for each patient.

Results: Select radiomic variables among the carotid artery, jugular vein, and thyroid groups exhibited overall significant differences when compared to the parathyroid adenoma data ($P < 0.05$). Further Tukey's *post hoc* analysis revealed that, when the parathyroid adenoma group was treated as the reference, 11/16 shape class, 16/18 first-order class, and 46/69 second-order class variables significantly differ from the carotid artery, jugular vein, and/or thyroid group(s). In addition, we found that the thyroid has distinct textural features compared to the parathyroid group, with 1/18 first-order and 19/69 second-order variables differing significantly between the two ($P < 0.05$). Notably, the texture variables such as dependence non-uniformity, long run emphasis, run percentage, run variance, and busyness exhibited the highest level of differences between the two groups ($P < 0.0001$).

Conclusion: The parathyroid adenoma group is associated with a unique set of radiomic variables in comparison to surrounding anatomy such as the carotid artery, internal jugular vein, and thyroid.

Relevance for Patients: The distinct, quantifiable differences in dimensional and textural features serve as a set of signature markers distinguishing parathyroid adenomas from their surrounding structures in 4D-CT. These attributes obviate the need for invasively locating parathyroid adenomas preoperatively, thereby enhancing the utilization rate of MIP, which has a favorable implication in the overall clinical outcomes.

1. Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by blood serum parathyroid hormone (PTH) levels >8 pmol/L and/or a serum calcium level higher than 2.60 mmol/L [1] caused by one or more of the parathyroid glands secreting an excess amount of PTH. The majority of cases are induced by a single parathyroid adenoma (89%)

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while a small number of cases are caused by multiglandular disease (MGD) (10%), or even more rarely parathyroid carcinoma [2]. PHPT may present asymptomatically or with a myriad of adverse symptoms, classically including renal, cognitive, and/or skeletal abnormalities [3].

Overall, PHPT is the third most common endocrine disorder following diabetes and thyroid disorders [4], thus making it a research area of significant importance, holding promise for improvement of treatment and quality of life. At present, parathyroidectomy is the only curative treatment of PHPT and is recommended in all patients with symptoms [5]. The two common surgical approaches to parathyroidectomy are a bilateral neck exploration (BNE) and a unilateral minimally invasive parathyroidectomy (MIP) [2]. In recent years, the surgical approach has widely changed in favor of MIP as this technique results in reduced surgical times, shorter hospital stays, decreased cost, improved cosmetic appearance, and reduced post-operative fibrosis of the neck, which is beneficial in the case of repeat surgery [1,6]. However, not all patients are candidates for this surgical approach. For example, in the case of MGD when all four glands may be involved, BNE is generally indicated [1]. This procedure involves a surgically intricate and demanding exploration of the delicate neck tissue to examine all four parathyroid glands.

Given the shortcomings and complexities of BNE, MIP is the preferred approach. Proceeding with MIP requires high-level, detailed imaging of the neck anatomy before surgery. At present, sestamibi and/or ultrasound are the most common modalities used for localization [7] but there is no universal protocol for pre-operative imaging. The modality used for imaging is typically based on the surgeon's and radiologist's preferences and knowledge. However, findings from past studies have underscored the importance of using specific imaging modalities according to the actual clinical scenarios. A comprehensive meta-analysis of patients using sestamibi SPECT/CT as a first-line approach for pre-operative imaging has shown a significantly low sensitivity and specificity of 65% and 80%, respectively, when compared to 4D-CT with a sensitivity and specificity of 81% and 89%, respectively [8]. In addition, past studies have shown that 4D-CTs have a concordance rate with intraoperative pathology results of 87%, which surpasses sestamibi and ultrasound with concordance rates of 26.9% and 26.1%, respectively [9]. The high concordance rate of 4D-CTs with intraoperative pathology findings highlights its increasing potential in PHPT detection because inaccurate pre-operative localization necessitates exploration of all parathyroid glands, triggering a shift of surgical approach from MIP to BNE. This data accords with recent studies showing that the mean number of glands explored during parathyroidectomy was significantly lower for patients who received a 4D-CT when compared to patients who were subjected to only nuclear imaging studies [10]. In the past, only difficult cases such as those with negative or discordant ultrasound and sestamibi scans or failed surgery called for the use of 4D-CT scans [11], but with recent findings of the superior efficacy of 4D-CTs, some medical centers have found success transitioning to a new protocol warranting a 4D-CT in replacement of sestamibi in the case of an inconclusive ultrasound finding [10].

There are other factors that might inform a provider's decision on the selection of imaging modality. For example, despite the low costs involved, ultrasounds provide poor imaging results for obese patients and have low sensitivity, and the quality of imaging findings is dependent on the technologist's expertise [11]. Comparatively, 4D-CTs, similarly to sestamibi, expose patients to ionizing radiation, involve higher upfront costs, and require specific radiologist expertise for interpretation.

To avoid the invasive path of BNE surgery, there is growing interest in developing the ability of 4D-CT to identify and localize parathyroid adenomas. By exploring the depth of potential of 4D-CT, it is possible to improve clinical outcomes by providing the necessary accurate pre-operative localization to allow for MIP. Thus, 4D-CT texture analysis has arisen as a particularly promising methodology to non-invasively identify parathyroid adenomas. For this reason, the purpose of this study is to correlate 4D-CT radiomic data to pathology-proven parathyroid adenomas to identify and quantitate select texture features that predict parathyroid adenomas with a high degree of confidence. Ultimately, this study aims to improve the reliability of parathyroid adenoma detection using quantitative CT imaging analysis [2,12].

2. Methods

2.1. Subjects

A total of 144 subjects with a history of a parathyroidectomy procedure for the removal of parathyroid adenoma between 2013 and 2023 were selected for this study through a search of our institution's database using mPower. Patients who received the final pathological diagnosis of parathyroid adenoma, based on intraoperative pathology-proven results of frozen section, were recruited. In addition, only subjects who received a 4D-CT scan of the neck for pre-operative detection and localization of parathyroid adenoma were selected. Patients who had undergone a single parathyroidectomy as well as multiple gland parathyroidectomy were selected. Cases with unsuccessful parathyroidectomy, negative findings, inaccurate localization of parathyroid adenoma on 4D-CT, thyroidectomy before preoperative 4D-CT, or unavailable pathology results were excluded. Fifty eligible cases were identified, of which 20 were randomly selected for inclusion. Figure 1 shows the flow chart of this study featuring the inclusion criteria. This study was approved by the institutional review board at the University of Chicago.

2.2. Image analysis

The 25-second arterial phase of each patient's 4D-CT neck scan (kVp: 120; mAs: 200; slice thickness: 3 mm) was used for analysis. Three anatomical structures (carotid artery, jugular vein, and thyroid gland) were chosen to differentiate from the parathyroid adenoma. An axial section of the 25-second arterial phases containing the largest area of each of the four structures was selected. Segmentation of the carotid artery, jugular vein, thyroid, and parathyroid adenoma was completed on the selected axial series of each patient using the 3D Slicer image computing platform. Figure 2 displays a representative resultant image

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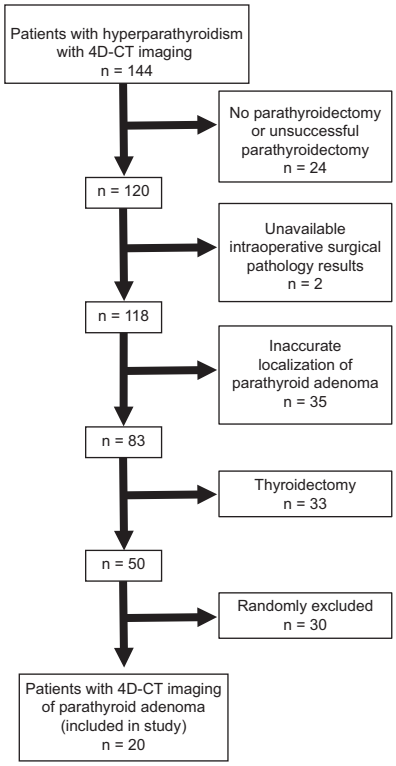

Figure 1. Flow chart of the present study and inclusion criteria.

after the segmentation technique was employed. The radiomic data were extracted and collected from the four structures of interest for each patient to be analyzed. Segmentation of a second axial section, from the same 25-second arterial phase scan, was completed for the carotid, jugular, and thyroid for the purpose of comparing the texture features to the previous segmentation to ensure consistency for each structure. The average of these two data points was taken for final analyses to ensure that the radiomic data are uniform between the two selected axial sections for each subject, reducing the possibility of artifacts or abnormalities impacting radiomic data.

2.3. Data analysis

Radiomic variables of the shape, first-order, and second-order classes were extracted from the segmentations of each of the 20 patients. In a categorical sense, data from the carotid artery, jugular vein, thyroid, and parathyroid adenoma were referred to as four distinct groups: carotid, jugular, thyroid, and parathyroid groups, respectively. Analysis of variance (ANOVA) was conducted to assess if there are statistical differences between the carotid, jugular, and thyroid groups when compared to the reference group, *i.e.*, parathyroid group. Subsequently, Tukey's HSD *post hoc* test was performed to compare differences in radiomic variables between specific anatomical structure groups. Variables that differ significantly between the parathyroid group and the other three groups were noted as radiomic variables that could potentially be used to differentiate the structures.

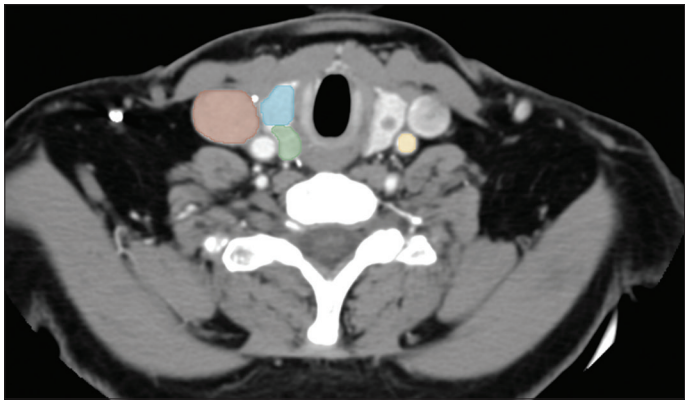

Figure 2. A representative resultant image following segmentation. Notes: Red represents jugular vein, yellow represents carotid artery, green represents parathyroid adenoma, and blue represents thyroid.

3. Results

A total of 144 patients were identified from the University of Chicago patient database for this study of which 20 were selected based on the exclusion criteria detailed in Figure 1. Patients who had undergone 4D-CT localization studies conducted between 2013 and 2023 were selected. The ages of the cohort analyzed ranged from 23 to 77 years with an average of 56.7 years. Patients of a range of races were analyzed, including White (40%), Black/African American (55%), and Asian/Mideast Indian (5%). The location of the parathyroid adenoma of interest for all patients falls into one of two categories: thyroid adjacent (85%) or ectopic/mediastinum (17.6%). Thyroid adjacent refers to any area adjacent to the thyroid gland, while ectopic/mediastinum is defined as any area not adjacent to the thyroid gland. Further details on cohort demographics can be found in Table 1.

Results of an ANOVA analysis revealed overall significant differences in select radiomic variables among the carotid artery, jugular vein, and thyroid groups when compared to the reference group, parathyroid adenoma data ($P < 0.05$). Upon completion of a follow-up Tukey's HSD *post hoc* test to compare specific groups, using the parathyroid group as the reference, we found that 11/16 shape class, 16/18 first-order class, and 46/69 second-order class variables significantly differ from the carotid artery, jugular vein, and/or thyroid group(s).

When comparing the thyroid to the parathyroid group, we found that the thyroid has distinct textural features, with 1/18 first-order and 19/69 second-order variables differing significantly between the two groups ($P < 0.05$). Notably, the texture variables such as dependence non-uniformity, long run emphasis, run percentage, run variance, and busyness exhibited the highest level of differences between the two groups ($P < 0.0001$). An isolated comparison revealed more subtle textural differences between the carotid artery group and the parathyroid group. We found that 14/18 first-order and 27/69 second-order variables presented significant differences between the two groups ($P < 0.05$), of which 12 variables were significant at the level of $P < 0.0001$. In our analysis of the internal jugular vein compared to

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the parathyroid group, we found that there were minimal textural distinctions between the two groups. We observed 5/18 first-order and 12/69 second-order variables differing significantly between the two ($P < 0.05$), of which only 2 variables were significant at the level of $P < 0.0001$. All significant variables and their respective level of significance can be found in Tables 2-4 for each anatomical group.

Table 1. Demographic information

Characteristics	N	%	Average
Age	20	-	56.71
Sex			
Male	8	40	-
Female	12	60	-
Race			
White	8	40	-
Black/African American	11	55	-
Asian/Mideast Indian	1	5	-
Hispanic/Latinx	0	0	-
Nodule location			
Ectopic/mediastinum	3	15	-
Thyroid adjacent	17	85	-

4. Discussion

The carotid artery and jugular vein are obvious anatomical landmarks and easily discernable from lesions for radiologists on 4D-CTs but not necessarily for computers. The long-term goal from this study is computer automated, texturally informed prediction and localization of parathyroid adenomas. With this in mind, radiomic data from the carotid artery and jugular vein, often in close proximity to parathyroid lesion and also hyperattenuating on post-contrast CT, is required to add to a model's inventory of patterns for predicting and differentiating lesions from surrounding anatomy with increased confidence.

Table 2. Predictive variables of significance for thyroid group

Variable	Variable class	Estimated difference in means	95% CI lower limit	95% CI upper limit	P_{adj}	Significance
Id	gclm	−1.83E-01	−2.96E-01	−7.02E-02	3.29E-04	**
Idm	gclm	−4.37E+00	−7.15E+00	−1.59E+00	5.28E-04	*
Idn	gclm	−5.45E+00	−7.64E+00	−3.27E+00	3.47E-08	**
InverseVariance	gclm	−4.04E+00	−6.51E+00	−1.57E+00	2.95E-04	**
DependenceNonUniformity	gclm	−4.55E+00	−7.24E+00	−1.85E+00	1.79E-04	****
GrayLevelNonUniformity	gclm	−4.40E+00	−7.05E+00	−1.75E+00	2.32E-04	***
SmallDependenceLowGrayLevelEmphasis	gclm	−2.12E+02	−3.22E+02	−1.01E+02	1.82E-05	**
LongRunEmphasis	gclm	−5.37E+00	−7.32E+00	−3.41E+00	1.92E-09	****
RunEntropy	gclm	−1.86E+02	−2.79E+02	−9.38E+01	6.76E-06	***
RunLengthNonUniformityNormalized	gclm	−2.16E+02	−3.29E+02	−1.03E+02	2.05E-05	***
RunPercentage	gclm	−6.04E+01	−1.20E+02	−7.89E-01	4.59E-02	****
RunVariance	gclm	−2.38E+07	−4.21E+07	−5.54E+06	5.42E-03	****
ShortRunEmphasis	gclm	−7.63E+01	−1.48E+02	−4.77E+00	3.20E-02	**
LargeAreaEmphasis	gclm	−6.47E+01	−1.29E+02	−3.60E-02	4.98E-02	*
LargeAreaLowGrayLevelEmphasis	gclm	−1.14E+07	−1.90E+07	−3.78E+06	1.05E-03	***
ZonePercentage	gclm	−6.56E-03	−1.18E-02	−1.34E-03	7.91E-03	*
ZoneVariance	gclm	−4.72E+01	−7.20E+01	−2.23E+01	2.19E-05	*
Busyness	gclm	−1.31E+02	−2.38E+02	−2.43E+01	9.84E-03	****
Coarseness	gclm	1.31E-02	4.04E-03	2.22E-02	1.65E-03	**
TotalEnergy	First order	−1.93E+02	−3.29E+02	−5.60E+01	2.23E-03	*
MajorAxisLength	shape	−6.67E-01	−9.75E-01	−3.59E-01	1.38E-06	****
Maximum2DDiameterColumn	shape	8.73E-02	8.15E-03	1.66E-01	2.48E-02	****
Maximum2DDiameterRow	shape	5.01E-02	1.36E-02	8.66E-02	3.03E-03	****
Maximum2DDiameterSlice	shape	−4.48E+00	−7.53E+00	−1.42E+00	1.37E-03	****
Maximum3DDiameter	shape	−9.51E-02	−1.77E-01	−1.34E-02	1.60E-02	****
MeshVolume	shape	−7.79E-01	−1.29E+00	−2.67E-01	8.38E-04	****
MinorAxisLength	shape	1.04E-01	2.61E-02	1.81E-01	4.12E-03	****
Sphericity	shape	−1.83E-01	−2.96E-01	−7.02E-02	3.29E-04	*
SurfaceArea	shape	−4.37E+00	−7.15E+00	−1.59E+00	5.28E-04	****
VoxelVolume	shape	−5.45E+00	−7.64E+00	−3.27E+00	3.47E-08	****

Notes: (i) Parathyroid group is the reference group for all comparisons in the table.
(ii) Positive values indicate that the mean of the parathyroid group is lower and *vice versa*.
(iii) ns: Not significant; *0.01< P < 0.05; ** 0.001< P < 0.01; *** 0.0001< P < 0.001; **** P<0.0001.

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Table 3. Predictive variables of significance for carotid group

Variable	Variable class	Estimated difference in means	95% CI lower limit	95% CI upper limit	P_{adj}	Significance
Elongation	shape	−2.93E-01	−4.06E-01	−1.80E-01	1.09E-08	****
MajorAxisLength	shape	3.16E+00	3.84E-01	5.95E+00	1.93E-02	*
Maximum2DDiameterSlice	shape	3.12E+00	4.22E-01	5.81E+00	1.68E-02	*
Maximum3DDiameter	shape	3.04E+00	3.94E-01	5.69E+00	1.79E-02	*
Sphericity	shape	−8.87E-02	−1.69E-01	−8.84E-03	2.35E-02	*
Percentile10	First order	−1.32E+02	−1.92E+02	−7.23E+01	8.13E-07	****
Percentile90	First order	−1.64E+02	−2.33E+02	−9.56E+01	1.17E-07	****
Entropy	First order	−3.87E-01	−7.71E-01	−2.90E-03	4.76E-02	*
InterquartileRange	First order	−1.64E+01	−3.06E+01	−2.26E+00	1.65E-02	*
Maximum	First order	−1.57E+02	−2.29E+02	−8.59E+01	9.24E-07	****
MeanAbsoluteDeviation	First order	−1.14E+01	−2.00E+01	−2.77E+00	4.70E-03	**
Mean	First order	−1.57E+02	−2.21E+02	−9.19E+01	8.14E-08	****
Median	First order	−1.68E+02	−2.35E+02	−1.00E+02	3.80E-08	****
Minimum	First order	−1.05E+02	−1.60E+02	−4.95E+01	2.19E-05	****
Range	First order	−5.29E+01	−1.03E+02	−2.97E+00	3.36E-02	*
RobustMeanAbsoluteDeviation	First order	−7.79E+00	−1.39E+01	−1.73E+00	6.21E-03	**
RootMeanSquared	First order	−1.56E+02	−2.21E+02	−9.18E+01	8.15E-08	****
Skewness	First order	6.40E-01	1.52E-01	1.13E+00	5.12E-03	**
Variance	First order	−1.21E+03	−2.25E+03	−1.75E+02	1.55E-02	*
Autocorrelation	gclm	−2.77E+01	−4.78E+01	−7.70E+00	2.77E-03	**
ClusterShade	gclm	4.17E+01	9.74E-01	8.24E+01	4.27E-02	*
ClusterTendency	gclm	−5.04E+00	−9.90E+00	−1.89E-01	3.86E-02	*
Contrast	gclm	−1.01E+00	−1.71E+00	−3.11E-01	1.64E-03	**
DifferenceAverage	gclm	−2.87E-01	−4.67E-01	−1.08E-01	4.02E-04	***
DifferenceEntropy	gclm	−4.52E-01	−6.71E-01	−2.34E-01	3.83E-06	****
DifferenceVariance	gclm	−5.71E-01	−9.44E-01	−1.98E-01	7.76E-04	***
Id	gclm	6.89E-02	1.77E-02	1.20E-01	3.79E-03	**
Idm	gclm	−2.93E-01	−4.06E-01	−1.80E-01	1.09E-08	**
JointAverage	gclm	3.16E+00	3.84E-01	5.95E+00	1.93E-02	***
SumAverage	gclm	3.12E+00	4.22E-01	5.81E+00	1.68E-02	***
SumSquares	gclm	3.04E+00	3.94E-01	5.69E+00	1.79E-02	*
GrayLevelVariance	gclm	−8.87E-02	−1.69E-01	−8.84E-03	2.35E-02	*
HighGrayLevelEmphasis	gclm	−1.32E+02	−1.92E+02	−7.23E+01	8.13E-07	**
SmallDependenceEmphasis	gclm	−1.64E+02	−2.33E+02	−9.56E+01	1.17E-07	****
HighGrayLevelRunEmphasis	gclm	−3.87E-01	−7.71E-01	−2.90E-03	4.76E-02	*
RunLengthNonUniformityNormalized	gclm	−1.64E+01	−3.06E+01	−2.26E+00	1.65E-02	**
ShortRunEmphasis	gclm	−1.57E+02	−2.29E+02	−8.59E+01	9.24E-07	***
ShortRunHighGrayLevelEmphasis	gclm	−1.14E+01	−2.00E+01	−2.77E+00	4.70E-03	**
SizeZoneNonUniformity	gclm	−1.57E+02	−2.21E+02	−9.19E+01	8.14E-08	***
SizeZoneNonUniformityNormalized	gclm	−1.68E+02	−2.35E+02	−1.00E+02	3.80E-08	****
SmallAreaEmphasis	gclm	−1.05E+02	−1.60E+02	−4.95E+01	2.19E-05	****
ZonePercentage	gclm	−5.29E+01	−1.03E+02	−2.97E+00	3.36E-02	****
Complexity	gclm	−7.79E+00	−1.39E+01	−1.73E+00	6.21E-03	*
Strength	gclm	−1.56E+02	−2.21E+02	−9.18E+01	8.15E-08	**
SmallDependenceHighGrayLevelEmphasis	gclm	6.40E-01	1.52E-01	1.13E+00	5.12E-03	**
GrayLevelNonUniformityNormalized	gclm	−1.21E+03	−2.25E+03	−1.75E+02	1.55E-02	*

Notes: (i) Parathyroid group is the reference group for all comparisons in the table.
(ii) Positive values indicate that the mean of the parathyroid group is lower and *vice versa*.
(iii) ns: Not significant; *0.01< P < 0.05; ** 0.001< P < 0.01; *** 0.0001< P < 0.001; ****P<0.0001.

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In addition, parathyroid lesions are most often located directly adjacent to the thyroid, making it difficult for radiologists and computers alike to distinguish between the two with a high level of confidence. Thus, our selection and comparison of the thyroid to parathyroid lesions in this study are particularly important. Our data suggest that parathyroid lesions are associated with a unique set of radiomic variables when compared to the thyroid. These distinct, quantifiable differences revealed will be of use in creating a texture signature specific to parathyroid adenomas. This signature could utilize dimensional and textural differences between the parathyroid adenoma and surrounding anatomy to create models that predict potential lesions and more precisely localize parathyroid adenomas.

Naturally, the next step in our application of this data is to investigate the performance of a parathyroid adenoma texture signature in models differentiating lesions from surrounding neck anatomy on 4D-CTs. For example, a recent study has had moderate success using imaging characteristics of parathyroid adenomas to predict the pathology of anterior mediastinal masses [13]. Another study achieved notable results by applying radiomic data extracted from parathyroid scintigraphy to algorithms to compare the utility and performance of different models [14]. Considering the recent success of other applications of radiomic data in the field, findings of this study are anticipated to make a meaningful contribution to future advances in parathyroid adenoma identification and localization. Ultimately, the ability to non-invasively localize parathyroid adenomas preoperatively could in turn translate to broader utilization of MIP, resulting in overall improved clinical outcomes [1,2].

Several limitations of this study should be acknowledged. The most prominent shortcoming of this study is that the relatively small sample size was n=20. In addition, the retrospective nature of the study and selection bias might influence the generalizability of the results. Further investigation is needed to validate our findings and warrant application in a clinical setting.

5. Conclusion

Our observations grounded in the statistical significance of several radiomic variables within the shape, first-order, and second-order feature classes in differentiating parathyroid adenoma from surrounding neck anatomy, such as carotid artery,

Table 4. Predictive variables of significance for jugular group

Variable	Variable class	Estimated difference in means	95% CI lower limit	95% CI upper limit	P_{adj}	Significance
Elongation	shape	−1.83E−01	−2.96E−01	−7.02E−02	3.29E−04	***
MajorAxisLength	shape	−4.37E+00	−7.15E+00	−1.59E+00	5.28E−04	***
Maximum2DDiameterColumn	shape	−5.45E+00	−7.64E+00	−3.27E+00	3.47E−08	****
Maximum2DDiameterRow	shape	−4.04E+00	−6.51E+00	−1.57E+00	2.95E−04	***
Maximum2DDiameterSlice	shape	−4.55E+00	−7.24E+00	−1.85E+00	1.79E−04	***
Maximum3DDiameter	shape	−4.40E+00	−7.05E+00	−1.75E+00	2.32E−04	***
MeshVolume	shape	−2.12E+02	−3.22E+02	−1.01E+02	1.82E−05	****
MinorAxisLength	shape	−5.37E+00	−7.32E+00	−3.41E+00	1.92E−09	****
SurfaceArea	shape	−1.86E+02	−2.79E+02	−9.38E+01	6.76E−06	****
VoxelVolume	shape	−2.16E+02	−3.29E+02	−1.03E+02	2.05E−05	****
Percentile10	First order	−6.04E+01	−1.20E+02	−7.89E−01	4.59E−02	*
Energy	First order	−2.38E+07	−4.21E+07	−5.54E+06	5.42E−03	**
Maximum	First order	−7.63E+01	−1.48E+02	−4.77E+00	3.20E−02	*
Mean	First order	−6.47E+01	−1.29E+02	−3.60E−02	4.98E−02	*
TotalEnergy	First order	−1.14E+07	−1.90E+07	−3.78E+06	1.05E−03	**
Idmn	gclm	−6.56E−03	−1.18E−02	−1.34E−03	7.91E−03	**
DependenceNonUniformity	gclm	−4.72E+01	−7.20E+01	−2.23E+01	2.19E−05	****
GrayLevelNonUniformity	gclm	−1.31E+02	−2.38E+02	−2.43E+01	9.84E−03	**
SmallDependenceLowGrayLevelEmphasis	gclm	1.31E−02	4.04E−03	2.22E−02	1.65E−03	**
LongRunHighGrayLevelEmphasis	gclm	−1.93E+02	−3.29E+02	−5.60E+01	2.23E−03	**
RunEntropy	gclm	−6.67E−01	−9.75E−01	−3.59E−01	1.38E−06	****
RunPercentage	gclm	8.73E−02	8.15E−03	1.66E−01	2.48E−02	*
ShortRunLowGrayLevelEmphasis	gclm	5.01E−02	1.36E−02	8.66E−02	3.03E−03	**
SizeZoneNonUniformity	gclm	−4.48E+00	−7.53E+00	−1.42E+00	1.37E−03	**
SmallAreaEmphasis	gclm	−9.51E−02	−1.77E−01	−1.34E−02	1.60E−02	*
ZoneEntropy	gclm	−7.79E−01	−1.29E+00	−2.67E−01	8.38E−04	***
Coarseness	gclm	1.04E−01	2.61E−02	1.81E−01	4.12E−03	**

Notes: (i) Parathyroid group is the reference group for all comparisons in the table.
(ii) Positive values indicate that the mean of the parathyroid group is lower and *vice versa*.
(iii) ns: Not significant; *$0.01<P<0.05$; **$0.001<P<0.01$; ***$0.0001<P<0.001$; ****$P<0.0001$.

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jugular vein, and thyroid, underline the projected utility of radiomic data in clinical localization of parathyroid adenomas. Used in conjunction with conventional indicators, radiomic data could prove to be a powerful tool in pre-operative localization of lesions, given that this line of questioning is further pursued with larger sample sizes and controlled research models.

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Conflict of Interest

The authors declare no conflicts of interest.

Ethics Approval and Consent to Participate

This work has been approved by the IRB. The IRB ID is IRB14-0749.

Consent for Publication

Consent was obtained through IRB.

Availability of Data

Data are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

The effects of lumbar self-sustained natural apophyseal glides on lumbar spine range of motion and hip muscle flexibility in asymptomatic college students: a crossover study

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ABSTRACT

Background: Patients with low back pain (LBP) tend to have prolonged treatment periods, which increase the cost of medical care. Several studies have reported that lumbar spine range of motion (ROM) and hip muscle flexibility are factors in LBP. Sustained natural apophyseal glides (SNAGs) have reportedly improved the lumbar spine ROM and hip flexibility of LBP patients. Moreover, self-SNAGs can be performed by the patients themselves.
Aim: This study aimed to evaluate the short-term effects of self-SNAGs on lumbar spine ROM compared to a repeated movement procedure in asymptomatic college students.
Methods: A prospective crossover study was conducted on 14 asymptomatic male college students. The asymptomatic participants performed self-SNAGs or repeated movements (i.e., three sets per day, 6 times a day over 1 week), and the compliance rate for both exercises was recorded. The lumbar spine ROM (i.e., flexion, extension, lateral bending, and rotation) was measured using the back ROM instrument, and hip muscle flexibility was measured using the Thomas test, heel-buttock distance, finger-floor distance, and straight leg raise test (SLR). Measurements were taken before commencement, immediately after, and 1 week later.
Results: Left lateral bending and left SLR were excluded from the between-group comparison (self-SNAG and sham) due to a carryover effect ($P < 0.05$). A comparison between the self-SNAG and sham groups displayed no significant differences in the lumbar spine ROM and hip muscle flexibility ($P > 0.05$).
Conclusion: Our study revealed that lumbar self-SNAGs had no significant effect on lumbar spine ROM or hip muscle flexibility in the short term, suggesting that such movements should be avoided when stretching to prevent LBP. However, this study did not include subjects with limited lumbar spine ROM and hip muscle flexibility due to pain, warranting further validation in future studies.
Relevance for Patients: The effects of lumbar self-SNAGs were similar to that of sham exercises in healthy individuals without joint ROM restrictions in the trunk or lower extremities due to LBP.

1. Introduction

Low back pain (LBP) is expected to develop in approximately 75.6% of adults at some point in their lives [1,2], and the recovery period is a significant financial burden even in developed countries [3-5]. LBP is commonly associated with decreased mobility of the lumbar spine [6-8], that is, decreased muscle flexibility around the trunk and hip joints [9-13]

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and the lumbar spine range of motion (ROM) [8]. Nonetheless, the causative factors (e.g., physical and functional) of LBP should be considered during the treatment process.

LBP is commonly treated with conservative management, which includes management exercise and manual therapy [14]. Among the different forms of manual therapy, mobilization with movement (MWM), devised by New Zealand physiotherapist Brian Mulligan [15,16], could effectively reduce pain and increase ROM at the affected joints of patients. A sustained natural apophyseal glide (SNAG) is an MWM technique that encourages the patient to move in a painful restricted direction. At the same time, the therapist applies a specific force to the spine through the spinous process in a direction parallel to the facet joint plane [17-26]. The applied force could subsequently eliminate pain during movement, and the pressure on the spinous process should be adjusted according to the patient's symptomatic response to the SNAG procedure to encourage more movements. This process is typically performed in three sets for 6–10 times [15,16].

Following a SNAG procedure, the patient is prescribed a self-SNAG as a home exercise to maintain or improve the pain-free ROM. A self-SNAG is essentially the same as the conventional SNAG technique, but it is performed solely by the patient. The manual force is applied to the spine by placing a thin strap under the spinous process of the affected area and applying cranial inclined pressure through the strap along the plane of the facet joint. With the force maintained by the strap, the patient repeats the active lumbar spine movement.

Previous studies have examined the effects of lumbar SNAGs in people with and without LBP with varying results [19,20,22]. Studies have been conducted to compare the effectiveness of manual therapy interventions on ROM in asymptomatic participants [27,28]. While SNAGs have reportedly improved ROM and flexibility [21], the effectiveness of self-SNAGs has not been reported, warranting further investigations in this regard.

Herein, we evaluated the effectiveness of self-SNAGs in healthy subjects based on their lumbar ROM and lower body flexibility. The purpose of this study was to compare the short-term effectiveness of lumbar self-SNAG with conventional trunk flexion in asymptomatic college students in terms of lumbar ROM and hip flexibility. We hypothesized that self-SNAGs could effectively increase patient compliance and subsequent improvements in LBP.

2. Methods

2.1. Participants

This study was registered in the University Medical Information Network (UMIN) Clinical Trials Registry (UMIN000040313). This study was approved by the ethics committee at the Saitama Medical University (929) and conducted in accordance with the Declaration of Helsinki. All participants agreed to sign an informed consent form.

Participants were recruited by means of advertising using posters placed across Saitama Medical University. We included 14 participants for the present study (average age: 21.0 ± 0.8 years; average height: 170.3 ± 4.3 cm; and average weight: 70.5 ± 13.3 kg). Participants were excluded if no consent was provided, if they had a history of LBP within the past 2 years, or could not perform the self-SNAG exercise. The study was a prospective randomized double-blinded crossover controlled study investigating the effect of self-SNAGs on lumbar spine ROM in asymptomatic college students.

2.2. Protocol

Each participant performed a warm-up, consisting of lumbar flexion, extension, lateral bending, and rotation movements that were performed 3 times in each movement direction. In this crossover study, different exercises were performed in Phases I and II. The envelope method was used to randomly allocate participants to either group A or B. In Phase I, Group A performed self-SNAG, while Group B performed the conventional trunk flexion. In the self-SNAG group (Group A), a specifically designed mobilization strap was hooked under the spinous process of the L4 lumbar with applied force in the cranial direction using both arms. While this force was maintained, the subject moved into trunk flexion as far as possible in the absence of pain (Figure 1A). The sham group performed repeated trunks forward as far as possible in the absence of pain without the strap (Figure 1B). The elbow and knee joints were flexed during the procedure. Both groups of subjects returned to their starting position immediately after flexing the lumbar spine. The exercises were performed in three sets 6 times/day over 1 week. The participants were requested to record the time of exercises on a specific table provided to them to evaluate the compliance rate. In Phase II, the exercises in Phase I were crossed over so that Group A performed the conventional trunk flexion while Group B performed the self-SNAG. The frequency of warm-ups and exercises and the evaluations were performed similarly to Phase I. The participants were instructed to record each exercise on a designated form daily for 1 week.

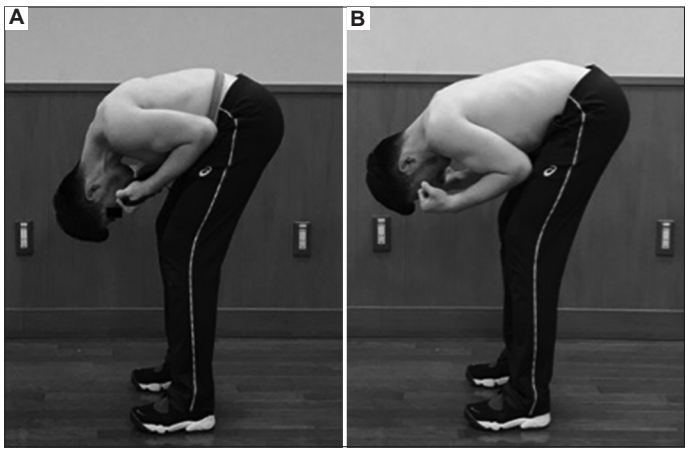

Figure 1. Exercises performed in the study. (A) In the self-sustained natural apophyseal glides group, the participants hooked a strap to the L4 spinous process and performed forward trunk flexion. (B) In the sham group, participants performed repeated forward trunk flexion without the strap.

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2.3. Measurement of the lumbar spine ROM

Measurements were taken before, immediately after, and 1 week after each exercise was performed. A back ROM (BROM) instrument (BROM Performance Attainment Associates, USA) was used on the twelfth thoracic spinous process for lumbar spine ROM measurement (Figure 2) [27,28]. ROM measurement was performed 3 times in each direction (i.e., flexion, extension, lateral bending, and rotation). The mean of three measurements was used for data analysis.

2.4. Other measurements

The Thomas test was performed on the participants in the supine position. The participant had one side of the hip joint maximally flexed, while the other side was extended. When the extended limb started to flex, the contralateral hip flexion angle was measured using an electrogoniometer with a minimum unit of 0.1°. The heal-buttock distance (HBD) was assessed with the subject in the prone position. The participant's knee was maximally flexed until firm resistance was observed. The distance between the heel and the buttocks was measured in mm. The finger-floor distance (FFD) was assessed in the standing position, and the participants were instructed to flex forward and maximally reach for the toes with their fingertips while maintaining the knees in extension. The distance between the fingertips and the floor was measured with a ruler in mm. The straight leg raise test (SLR) was evaluated with the subject in the supine position. The hip joint was flexed while maintaining the participant's knee joint in extension, and the range of hip flexion was recorded in degrees using an electrogoniometer. The mean of three measurements was used for data analysis.

2.5. Data analysis

All data were analyzed with SPSS Version 27.0 (IBM Corporation, USA). Either an unpaired *t*-test or Mann-Whitney *U* test was used to compare the effects in Phase I and performed both immediately and 1 week after intervention (i.e., self-SNAG or repeated movement). Likewise, either a paired *t*-test or Wilcoxon rank sum test was used to determine whether the intervention effect in Phase I was washed out and was performed based on the baseline values of Phases I and II. If the intervention effect of Phase I was washed out, we compared the intervention effect both immediately and 1 week after intervention between the self-SNAG (n = 14) and sham (n = 14) groups using an unpaired *t*-test or Mann–Whitney U test. If the intervention effect of Phase I was not washed out, the endpoint was excluded from this study. Significant differences were set at a level of 0.05.

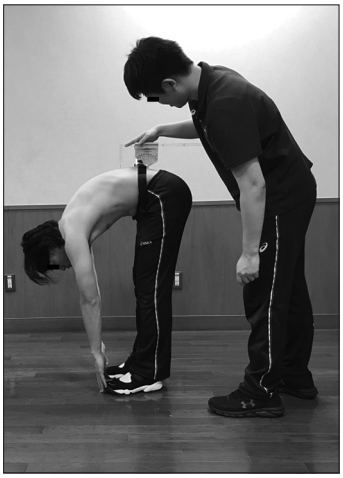

Figure 2. Measurement of the lumbar spine flexion range of motion (ROM) using a back ROM instrument.

3. Results

Our findings revealed that the compliance rate for performing the exercises over the 1-week intervention period in the self-SNAG and sham groups was 95%. We observed no significant differences in the exercise compliance rate between the groups both immediately and 1 week after Phase I intervention ($P > 0.05$).

However, there was a significant difference in left lateral bending and left SLR in group B for the pre-intervention comparison of Phases I and II (Tables 1 and 2). Therefore, lateral bending and left SLR were deemed as washed out and were excluded from the study.

In Phase I, self-SNAG was performed in Group A, and conventional trunk flexion was performed in Group B. Subsequently in Phase II, the exercises in Phase I were replaced, where Group A performed conventional trunk flexion and Group B performed self-SNAG. The difference in averages (of lumbar ROM and other measurements) between both groups in Tables 1 and 2, respectively, are expressed as mean ± standard deviation.

In addition, we observed no significant differences in the lumbar ROM (i.e., flexion, extension, right lateral bending, and rotation) and other measurements (Thomas test, HBD, FFD, and right SLR test) both immediately and 1 week after intervention (Tables 3 and 4, respectively).

Table 1. Differences in the lumbar ROM for Groups A and B between Phases I and II

Group	Measurement	Difference	*P*-value	95% CI
A (n=4)	Flexion	2.3±3.3	0.26†	−2.97, 7.47
	Extension	2.4±1.8	0.45‡	N/A
	Right lateral bending	1.2±2.1	0.35†	−2.23, 4.56
	Left lateral bending	1.7±3.5	0.41†	−3.85, 7.18
	Right rotation	−1.3±2.1	0.32†	−4.56, 2.06
	Left rotation	0.0±0.9	1.00†	−1.50, 1.50
B (n=10)	Flexion	1.8±4.5	0.24†	−1.44, 5.04
	Extension	3.1±0.2	0.57‡	N/A
	Right lateral bending	−0.8±3.0	0.43†	−2.98, 1.38
	Left lateral bending	−2.1±1.8	0.01†	−3.48, −0.79
	Right rotation	−1.2±2.2	0.12†	−2.80, 0.40
	Left rotation	−1.1±2.0	0.12†	−2.47, 0.34

Note: †*P*-value was determined via student's *t*-test; ‡*P*-value was determined via Wilcoxon rank sum test.
Abbreviations: CI: Confidence interval; N/A: Not applicable; ROM: Range of motion.

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4. Discussion

The purpose of this study was to evaluate the effects of self-SNAGs compared to conventional repeated movements (i.e., trunk flexion) on the lumbar spine ROM and hip muscle flexibility both immediately and 1 week after intervention.

Table 2. Differences in the other measurements for Groups A and B between Phases I and II

Group	Measurement	Difference	*P*-value	95% CI
A (*n*=4)	Right-side Thomas test	0.6±0.8	0.26†	−7.00, 1.80
	Left-side Thomas test	0.2±0.9	0.52†	−0.47, 0.85
	Right HBD	−0.1±0.4	0.97†	−0.71, 0.69
	Left HBD	0.1±1.5	0.86†	−0.96, 1.13
	FFD	−4.0±13.8	0.60†	−25.98, 17.98
	Right SLR	−7.8±21.5	0.28†	−23.23, 7.57
	Left SLR	−7.0±15.4	0.43†	−31.58, 17.58
B (*n*=10)	Right-side Thomas test	−10.5±19.7	0.13†	−24.53, 3.60
	Left-side Thomas test	−55.8±112.5	0.39†	−234.83, 123.16
	Right HBD	−15.9±26.3	0.88†	−34.72, 2.92
	Left HBD	70.9±10.3	0.14‡	N/A
	FFD	66.6±6.5	0.80‡	N/A
	Right SLR	71.6±11.8	0.07‡	N/A
	Left SLR	67.0±10.1	0.05‡	N/A

Note: †*P*-value was determined via student's *t*-test; ‡*P*-value was determined via Wilcoxon rank sum test.
Abbreviations: CI: Confidence interval; HBD: Heel-buttock distance; FFD: Finger-floor distance; SLR: Straight leg raise test; N/A: Not applicable.

For lumbar spine ROM (flexion, extension, right lateral bending, and rotation), no intervention effect was observed either immediately or 1 week after the intervention. Although no studies have previously investigated the effects of self-SNAGS, studies on the effects of lumbar SNAGs in asymptomatic participants have also reported no significant differences in lumbar spine ROM [26]. Taken together, both SNAG and self-SNAG do not affect the ROM of pain-free people, suggesting that SNAGs target pain through a different mechanism instead of the lumbar ROM *per se*. In symptomatic people with LBP, a pain-free mobilization force applied during the self-SNAG or SNAG procedure is thought to improve the gliding property of the facet joints [19], thereby reducing pain and the fear of movement during exercise. Since the participants of this study were asymptomatic, the lumbar ROM was not restricted by pain and could only improve through changes in the viscoelastic properties of the joints and soft tissue. However, there were no significant differences between the sham and self-SNAG procedures.

Similarly, there were no changes to muscle flexibility around the trunk and pelvis following the application of self-SNAGs. The Thomas test, HBD, FFD, and right SLR reported no intervention effect both immediately and 1 week after the intervention. In a previous study, SNAGs were performed on the lumbar spine of LBP participants in combination with trunk flexion, and the findings revealed improvements in the flexibility of the back and hip muscles [22]. In addition, the stiffness of the multifidus and erector spinae muscles (after SNAGs) was measured using shear wave elastography and reported a decrease in muscle hardness,

Table 3. Lumbar spine range of motion measurements immediately and 1 week after intervention

Intervention time	Measurement	Group	Lumbar spine range of motion				
			Mean±SD	*P*-value	95% CI	Effect size	Power (1–β)
Immediately after	Flexion	Self-SNAGs	10.5±3.0	0.66§	−3.17, 2.03	0.15	0.07
		Sham	11.0±3.6				
	Extension	Self-SNAGs	4.6±2.8	0.95	N/A	0.00	0.05
		Sham	4.6±3.2				
	Right lateral bending	Self-SNAGs	26.8±3.8	0.12§	−0.58, 5.01	0.62	0.35
		Sham	24.6±3.3				
	Right rotation	Self-SNAGs	8.6±2.6	0.25§	−0.92, 3.40	0.47	0.23
		Sham	7.3±2.9				
	Left rotation	Self-SNAGs	9.0±2.9	0.10§	−0.34, 3.96	0.65	0.38
		Sham	7.2±2.6				
One week after	Flexion	Self-SNAGs	9.6±2.7	0.50§	−3.50, 1.74	0.27	0.11
		Sham	10.5±3.9				
	Extension	Self-SNAGs	4.4±2.0	0.54	N/A	0.33	0.13
		Sham	5.2±2.8				
	Right lateral bending	Self-SNAGs	25.6±3.4	1.00	N/A	0.17	0.07
		Sham	25.0±3.6				
	Right rotation	Self-SNAGs	8.0±3.1	0.55§	−1.71, 3.14	0.26	0.10
		Sham	7.2±3.1				
	Left rotation	Self-SNAGs	8.4±2.4	0.30§	−1.00, 3.10	0.41	0.18
		Sham	7.3±2.9				

Note: §*P*-value was determined via the unpaired *t*-test; *P*-value was determined via the Mann-Whitney U test.
Abbreviations: SD: Standard deviation; CI: Confidence interval; SNAGs: Sustained natural apophyseal glides; N/A: Not applicable.

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Table 4. Other measurements immediately and 1 week after intervention

Intervention time	Measurement	Group	Measurement				
			Mean±SD	*P*-value	95% CI	Effect size	Power (1–β)
Immediately after	Right-side Thomas test	Self-SNAGs	3.8±1.0	0.21§	−0.68, 0.52	0.82	0.55
		Sham	4.5±1.7				
	Left-side Thomas test	Self-SNAGs	4.0±1.5	0.93§	−1.17, 1.07	0.03	0.05
		Sham	4.1±1.4				
	Right HBD	Self-SNAGs	90.9±37.1	0.94§	−33.81, 31.38	0.05	0.05
		Sham	92.1±46.3				
	Left HBD	Self-SNAGs	91.5±41.9	0.97§	−35.07, 33.79	0.82	0.55
		Sham	92.2±46.6				
	FFD	Self-SNAGs	−8.1±111.2	0.89§	−85.80, 75.04	0.03	0.05
		Sham	−2.7±95.2				
	Right SLR	Self-SNAGs	68.7±6.3	0.43	N/A	0.05	0.05
		Sham	67.1±6.1				
One week after	Right-side Thomas test	Self-SNAGs	3.8±1.2	0.87§	−0.08, 0.47	0.92	0.65
		Sham	3.8±1.3				
	Left-side Thomas test	Self-SNAGs	4.2±1.3	0.91§	−1.16, 1.30	0.30	0.12
		Sham	4.1±1.8				
	Right HBD	Self-SNAGs	79.1±33.3	0.43§	−39.56, 17.46	0.02	0.05
		Sham	90.1±39.8				
	Left HBD	Self-SNAGs	82.9±37.7	0.64§	−37.02, 23.17	0.92	0.65
		Sham	89.8±39.7				
	FFD	Self-SNAGs	1.5±86.7	0.96§	−69.38, 65.62	0.30	0.12
		Sham	3.4±87.1				
	Right SLR	Self-SNAGs	68.1±4.6	0.53§	−2.61, 4.95	0.02	0.05
		Sham	67.0±5.2				

Note: §*P*-value was determined via the unpaired *t*-test; *P*-value was determined via the Mann–Whitney U test.
Abbreviations: SD: Standard deviation; CI: Confidence interval; SNAGs: Sustained natural apophyseal glides; N/A: Not applicable; HBD: Heel-buttock distance; FFD: Finger-floor distance; SLR: Straight leg raise test.

which could be attributed to the presence of pain [29]. Pain is likely to increase the muscle tone of the muscles around the spine and pelvis which influences flexibility [30]. The effectiveness of SNAG in improving flexibility and reducing pain is influenced by the subject's initial flexibility limitations and pain intensity. In addition, the accuracy of the technique and the duration of the intervention may have an impact. It may be difficult to determine the effect of treatment in patients with milder symptoms. Notably, it is unclear whether SNAG practitioners are members of the Mulligan Concept Teacher Association or Certified Mulligan Practitioners, or whether their skills in performing SNAGs are well established. Furthermore, patients would display a poorer compliance rate at longer intervention periods or when their symptoms started to improve, thereby affecting the effectiveness of the study. The elimination of pain through the SNAG technique, together with repeated active movement, could explain the improvement in muscle flexibility. In the absence of pain, repeated movement with or without the self-SNAG appears to have no beneficial effect on muscle flexibility. Despite our results indicating that self-SNAG did not affect lumbar ROM and hip muscle flexibility, previous studies have suggested that it could alleviate pain.

Moreover, the lack of effect observed in this study could be attributed to the different positions used in previous SNAG studies. The self-SNAG procedure in this study was performed in a standing position, while SNAGs were performed in a sitting position in previous studies, of which demonstrated positive effects [19-21,24-26]. The different effects between our study and previous reports could also be associated with the force generated by an experienced therapist for SNAG versus a self-SNAG where the force relies on the lumbar self-SNAG strap (typically lesser than that applied by the therapist's hands in a regular SNAG), suggesting that self-SNAGs may be less effective in increasing muscle flexibility of the lower limbs when compared to SNAGs and warranting further investigation in a symptomatic population. Our study also demonstrated a carryover effect in left lateral bending and left SLR. Although we did not examine the dominant arm in this study, we hypothesized that right-handed subjects tended to pull harder on the right strap, strongly affecting the left lumbar rotation and left SLR and resulting in longer-lasting effects.

This study also compared the effects of lumbar spine flexion, extension, right lateral flexion, right rotation, and left rotation ROM, and the Thomas test, FFD, and right SLR exhibited a trend toward higher lumbar spine ROM or hip muscle flexibility immediately after intervention. This study was based on a crossover study in which manual therapy [31,32] and myofascial release [33] were performed on LBP participants, and a 1-week

washout was established after no significant differences were observed. Hatano *et al.* [32] reported that the effect of 300 s of static stretching was equivalent to 20 min of static stretching. Therefore, it is suggested that regular stretching by a therapist and continued stretching are important to sustain the effects of the intervention. However, LBP has a high incidence rate and is expensive to treat [34], making it difficult for patients to visit the clinic regularly. Nonetheless, the duration of treatment for LBP can be shortened when the compliance rate of self-exercise is high [34]. However, in this study, the self-SNAGs and sham groups displayed a decreasing trend in efficacy 1 week after the intervention compared to immediately after the intervention, even though the compliance rate was 95% for both groups. This could be due to the fact that the self-exercise for evaluating the intervention effects immediately after the intervention was performed under the supervision of the researchers, whereas the self-exercise for the comparison of intervention effects 1 week after the intervention was performed at home and unsupervised. Nicolson *et al.* [35] reported that the correct implementation of the self-exercise overestimates the intensity and frequency of the exercises. When performing self-SNAGs at home, it is unclear whether the subject can apply the belt in the correct position, pull the belt with the correct force, and balance the left and right sides of the belt as instructed, and these actions depend on the subject's moderation. Therefore, it is necessary for the therapist to accurately set the intensity and number of times when teaching self-exercise as it is difficult to precisely reproduce the self-exercise without proper instructions and guidance.

Nonetheless, this study had several limitations. First, the asymptomatic adult male college students were in a narrow age range of 21.0 ± 0.8 years old, and future studies should investigate a population with a wider age range. Besides that, there could have been variations in the application and amount of force applied by the participant when performing self-SNAG. Furthermore, this study did not evaluate the alignment of the vertebral column because the subjects were asymptomatic. The vertebral column is involved in the balance of the hip bones in the sagittal plane and should be assessed as well to better evaluate the effectiveness of self-SNAG [36]. Finally, the sample size of this study was calculated using G*Power 3.1.9.2 before the start of the study, and the sample size was 30 (α = 0.05; 1–β = 0.8; effect size[25] = 1.0778376). However, it became difficult to recruit participants for this study due to the COVID-19 pandemic during the study period.

5. Conclusion

Although SNAG is thought to alleviate pain and improve movement, this study revealed that SNAG was not effective in the asymptomatic subjects of this study, as observed from the ROM and flexibility in the lower back and lower extremities. To interpret the results of this study (i.e., low intervention effect on asymptomatic individuals), the low effect size should also be considered. Based on our present findings, we aim to investigate the effects of self-SNAG on LBP and flexibility by implementing SNAG alone or a combined SNAG and self-SNAG intervention in patients with LBP in future studies.

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Conflict of Interest

The authors declare no competing interests.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee at the Saitama Medical University (929). All participants agreed to sign an informed consent form.

Consent for Publication

All participants agreed to sign an informed consent form to use their data for this study.

Availability of Data

Not applicable.

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