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Radiology, Diagnostic Imaging and Instrumentation

Peritoneal Hydatid Cyst Rupture

Cervical Lymphangiomas in Children

Highlights

Evaluation of Avascular Necrosis

Study of Lung Computerised Tomography

Discovering Thoughts, Inventing Future

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Cervical Lymphangiomas in Children: Non-Surgical Treatment with Focus on Sclerotherapy. Literature Review

By Pietro Pitrone, Donatella Di Fabrizio, Antonino Cattafi, Alessandra Coglitore, Maria Ludovica Carerj, Italo Giuseppe Bellone, Enrico Monsù, Giuseppe Nirta, Dora Bonanno, Carmelo Romeo & Pietro Impellizzeri

University of Messina

Abstract- *Objectives:* To discuss the non-surgical strategies for the management of cervical lymphangiomas in children, with particular attention to sclerotherapy.

Methods: A literature review of the last fifteen years about sclerotherapy of cervical lymphangiomas in children was performed and the main sclerosing agents were reported, highlighting the nature, the mechanism of action and the rates of success, recurrences and complications related to each and every substance; furthermore, the several steps of the procedure are illustrated. Alternative approaches are also mentioned.

Results: 47 articles were collected, mostly dealing with sclerotherapy with OK-432, bleomycin/pingyangmycin and doxycycline; other potential substances include, above all, sodium tetradecyl-sulphate and ethanol. Laser therapy and radio-frequency ablation are valid options in case of mucosal micro-cystic lesions; oral medications (e.g. Sirolimus) and the newest target-therapies are added to local treatments in some Series.

Keywords: *cervical lymphangiomas, surgery, sclerotherapy, sclerosing agents.*

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Conclusions: Despite no univocal guidelines and the most recent "multi-approach" strategies, sclerotherapy represents the main non-surgical treatment for cervical lymphangiomas (especially when dealing with macro-cystic or mixed varieties) in children, and sometimes the first-line strategy. OK-432, bleomycin/pingyangmycin, doxycycline and sodium tetradecyl-sulphate represent the agents of choice, proving feasible with either micro-cystic lesions in several studies.

Advances in knowledge: Given the rarity of the disease, no large study fully reporting the results of sclerotherapy in the treatment of cervical lymphangiomas in children within the last years is available.

Keywords: cervical lymphangiomas, surgery, sclerotherapy, sclerosing agents.

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I. Background

Lymphangiomas (Lms) or, as recently preferred (according to ISSVA classification for vascular anomalies 2018), "lymphatic malformations" consist of lymphatic channels anastomosis and cystic spaces, as a result of abnormal connections between the lymphatic and venous systems or abnormal development or location of lymphatic vessels. Their incidence is 1/12000 births, accounting for 6% of all benign lesions of infancy and childhood. Cervico-facial lesions represent 75% of the cases and 80-90% become symptomatic within the first 2 years of life (both sexes equally affected) because of their progressive enlargement with growth. Many of them are congenital and often associated with other vascular or chromosomal abnormalities (e.g. Turner syndrome), without a clear familial tendency; however, they may arise or increase in size due to trauma, inflammation or lymphatic obstruction. Spontaneous regression within 18-24 months is documented in 1.6-16% of cases. Classification into macro-cystic, micro-cystic and mixed is based upon the diameter of the cysts. Presentation varies from asymptomatic, soft, not compressible, trans-illuminant neck tumefaction to dysphagia, malocclusion, sleep disordered breathing, respiratory distress and recurrent infections [1]. Since they are not encapsulated, they show infiltrative growth and often are not dissociable from airway, nerves and blood vessels [2].

Histology is similar to hamartomas, although some state a lymphangiectasic or neoplastic nature, without any malignant potentiality [3]. Ultrasonography documents mono- or multiloculate fluid-superfluid lesions with a substantial lack of flow with Doppler mode *(figure/patient 1-2)*. Computer Tomography (CT) describes low attenuation masses with occasional fluid level and minimum septal and peripheral enhancement. Magnetic resonance imaging (MRI) detects iso- or hypo-signal on T1-weighted sequences and hyper-signal on T2-weighted sequences, a halo of enhancement around the septa of macro-cystic lesions and peri lesional lymphoedema *(figure/patient 2-3)* [4].

While small and asymptomatic lesions might benefit from purely conservative management (e.g.

compression, analgesia), larger and symptomatic (e.g. dysphagia, dyspnoea) malformations would require non-conservative treatment; this implies a multi-disciplinary approach (surgical, radiological, physician's) which varies according to each patient's characteristics and lesions, considering the lack of univocal indications for treatment as well as all those issues related to the young age of the patient (psychological or parental concern). Traditional surgical treatment has been considered for many years the gold standard for lymphatic malformations and is still considered the most definitive solution; however, as lymphangiomas are infiltrative, a complete eradication is often impossible [5]. This explains the relatively high percentage of recurrences (up to 27%) and intraoperative risks, with a mortality rate of 2-6%. At the present, surgery is indicated for lesions larger than 3 cm (sometimes for debulking, followed by sclerotherapy), with progressive growth, bone erosion, dyspnoea or dysphagia [6]. It is also advocated for the resection of remaining fibrotic tissue after sclerotherapy or as a first-line therapy for lesions outside the cervico-facial region, associated with few intraoperative risks or aesthetic sequelae [7]. Minor complications include lymphorrhea, keloids, dehiscences, fistulas, and the need of a prolonged post-operative drainage from the wound, with an associated risk of infection[8].

The aim of the study was to review and discuss the non-surgical strategies for the management of cervical lymphangiomas, with particular attention to the sclerosing agents.

II. Material and Methods

All relevant articles including "cervical lymphangiomas" or/and "sclerotherapy" were searched on PubMed, Cochrane and Embase platforms. Inclusion criteria were: (1) studies published mostly within the last fifteen years, (2) studies including paediatric population, (3) studies reporting advantages, success rate, recurrence rate, complications and dose for each and every sclerosing agent, (4) studies written in English. In addition, instructions for the procedure of ultrasound or CT-guided sclerotherapy and other alternative treatments were considered.

III. Results

As many as 47 articles dealing with sclerotherapy of cervical lymphangiomas in children were collected. Beside short information about the first therapeutical approaches, laser therapy, radiofrequency ablation and oral medications (e.g. Sirolimus) including the newest target-therapy, a much larger knowledge was obtained about sclerotherapy's rationale, steps and agents, from the most employed (OK-432, bleomycin/ pingyangmycin, doxycycline, sodium tetradecyl-sulphate) to potential alternatives (such as ethanol) or occasionally-used substances (e.g., acetic acid, Ethibloc, Tissucol, Polidocanol).

IV. Discussion

Historically, the first non-surgical treatments for cervical lymphangiomas were with simple direct drainage, aspiration and radiation. A combined radio-chemotherapeutic approach was performed in selected cases of hemolymphatic malformations [1].

Laser therapy is an alternative to surgery for small and superficial (cutaneous or oral) lymphangiomas or for debulking of invasive, large and non-excisable lymphangiomas. Traditional techniques consist of the resection and removal by photocoagulation with argon, carbon dioxide, Nd:Yag, KTP and diode lasers. Pain, oedema and swelling are associated with complete healing at 6-8 weeks, although a scar may persist for many years. Ten to 33% of cases are complicated by intraoperative bleeding or nerve injury. Namour and coll suggested a peculiar therapeutic method for debulking of invasive and extensive lesions within oral soft tissues, preventing the patients from mutilation. A CO2 laser machine with output power of 2W in defocus and in non-contact mode for at least 3 min is used, with a distance between the laser handpiece and the tissular impact point around 6 cm, the delivered focal point at 0.3 mm, the effective spot diameter range at tissue at about 2 cm (power density = 0.63W/cm2) and the estimated energy density range at 114.65–191 J/cm2. This protocol does not cause disintegration/vaporisation but only overheating, with subsequent fibrous healing. Out of seventeen patients, only three (18%) experienced recurrence and no major complication (embolism, infection or mutilation) occurred. Other minor treatments include cryotherapy, diathermy and electro-cautery [9].

Another example of local treatment is offered by radio-frequency ablation (RFA) or hypothermic ablation, destroying lesions at lower temperatures (40-70°) with subsequent lower damages within surrounding tissues. Micro-cystic lymphangiomas in mouth, throat, pharynx, retro-pharynx and tongue may benefit from RFA, which also helps to stop accidental or intra-operative bleedings [10].

Sclerotherapy is nowadays largely employed in case of macro-cystic or mixed lymphangiomas, where the size of the cysts allows them to be punctured and a wider distribution of the agent is achieved. However, OK-432, bleomycin and above all doxycycline have recently proved effective also with micro-cystic variety [2]. The rationale comes from the observation that lymphangiomas can reduce their size or regress after a spontaneous infection, probably due to the destruction of the epithelium, reduction of lymph production and collapse of the cyst: thus, the idea of adopting sclerosing agents to mimic such an effect. Puncture of

the dominant cyst (or more, in case they are non-communicating) with a fine needle (20 G or more) is followed by aspiration (in order to enhance the SA effect) and injection, in one or more times, of the sclerosing agent, using the same amount as the aspirated fluid (if impossible, half of the lesion's volume). It can be repeated in case of partial response or whenever more administrations are chosen, each session being separated by weeks up to a month. General or loco-regional anaesthesia is preferred in children or uncooperative patients and in adults or small cystic malformations, respectively; the patient's position is changed many times to favour a uniform distribution of the agent and the treatment lasts up to two hours. A postoperative compressive bandage is advised in order to increment the time of contact between the solution and the cyst's wall and to prevent seroma formation, bleeding or effusion of the SA. The procedure can be performed under ultrasound or CT: the first is cheaper, more available, does not employ ionising radiations (thus being advisable in children and young adults), defines better the different components within the lesion, grants different cranio-caudal angles and reduces the risk of accidental puncture of large blood vessels; however, it is operator-dependent and offers a narrow field of view, with the risk of missing some important findings, especially at the post-procedure check. CT instead is easier to perform and provides a more panoramic view but implies radiation and the needle path to lie on the axial plane with its full length [1]; a detailed example of this procedure is offered in *figure (patient) 4,* whereas *figures (patients) 5 and 6* show examples of successful outcomes comparing lymphangiomas before and after sclerotherapy. Fluoroscopic guidance is also reported, especially in case of the most superficial lesions, with the possibility to inject contrast medium into the lesion in order to highlight communications between the intra-lesional spaces and establish the amount of SA to be used [4]. Complications include intraoperative bleeding (due to their dysplastic nature), accidental injuries to nerves, vessels, organs and other tissues (due to extravasation), peri-lesional fibrosis and aesthetic sequelae (due to necrosis followed by second-intention reparation), dose-dependent cardio-pulmonary toxicity (especially with bleomycin) and acute respiratory insufficiency (with large lymphangiomas undergoing inflammation, necrosis and quick volumetric expansion); the latter could be managed with dexamethasone or, preferably, avoided by splitting the treatment in more sessions [7]. An example of follow-up program would consist of a clinical examination after one to three weeks, ultrasonography after six to twelve weeks and then (depending on the results of ultrasound) MRI, unless evidence of early recurrence or any other complication occurs [8]. A review by Adams et al didn't prove the superiority of sclerotherapy over surgery but showed it was the treatment of choice in most major paediatric vascular anomaly centres: surgery was reserved for refractory cases, with sclerosing agents not improving either clinics or aesthetics, micro cystic lesions or those associated with life-threatening airway obstruction. Nowadays there are no worldwide-accepted guidelines and patient selection seems to guide the choice. In addition, neither surgery nor sclerotherapy can guarantee complete healing with just one session: it is actually advisable to perform multiple treatments or combine them[1].

When dealing with sclerotherapy, the first substances to be employed (with poor results) were boiling water, quinine, urethane, iodine tincture, nitromin, sodium morrhuate 5% and acetic acid 40 to 50%, the last two with little more reference in literature [1]: sodium morrhuate is currently employed for orbital lymphangiomas; acid acetic causes an area of coagulative necrosis much wider than ethanol (with pain and tingling sensation) but with a faster and more complete regression [11]. Many others sclerosing agents (SA) were used by the years, but no guidelines are currently available due to the infrequency of the disease and the limited studies; therefore, the decision is based on Centres and operators according to their experience and the availability and side-effects of the agents [12].

OK-432 (Picibanil; *table 1*) was first used by Ogita in 1987 [13]. It comes from the lyophilisation of a mixture of Streptococcus pyogenes and G-Penicillin. It favours the production of IL-1, IL-2, IL-6, INF-ɣ and TNF, the activation of neutrophils, macrophages, NK and T lymphocytes, the apoptosis of the epithelium and increases the permeability of the endothelium, accelerating the lymphatic fluid drainage. Compared to others SA, OK-432 is associated with a lower risk of extravasation and subsequent peri-lesional fibrosis, systemic toxicity or/and aesthetic sequelae [14]. In addition, according to both Efe and Hazim (2016), the lesion is still feasible for surgery even after sclerotherapy failure [15,16]. Luzzato et al (2000) confirmed its usefulness for residual and recurrent lesions, as well as the low invasivity and scarring [17]. Sichel et al (2004) agreed with the lack of a significant peri-lesional fibrosis [18]. The percentage of success is 50-92% (remaining high even with repeated injections), with 43% of complete and 29,3% of partial remissions [19], whereas the frequency of the recurrences is around 11% [15] and the complications are rare and mostly local (pain, heat, induration, erythema, oedema, swelling, aesthetic sequelae, swallowing difficulty and odynophagia, infections) with sporadic fever, sepsis and shock, especially in patients with allergy for G penicillin [1]. Yoo et al (2009) stressed the safety of OK-432, reporting minor complications only and stating a high long-term efficacy [20]. Rebuffini et al (2012) also reported anaemia and a transitory increase of platelets'

concentration [21]. The low systemic toxicity allows OK-432 to be used also with micro-cystic (where the percentage of success reaches nearly 50%) or intra-parenchymal components, where the risk of tissue absorption is the most [22]. Ruiz et al (2004) confirmed its feasibility for micro-cystic lesions, as well as those associated with a risk of airway obstruction [23]. Ogita recommends 0,1 mg/10 cc with a maximum of 20 mL of solution or 0,2 mg of substance [24]. Despite all its advantages and proven effectiveness, however, OK-432 is less and less employed in the UK.

Bleomycin sulphate *(table 2)* is an antibiotic with antitumour action, inhibiting DNA synthesis. Tanigawa et al were the first to employ it as a sclerosing agent, reporting a lower recurrence rate than surgery and stating the possibility to use it in case of surgery failure [25]. Sung et al also used it for debulking of unresectable lesions [26]. It shows good responsivity (88%), a discrete frequency of complete remissions (36-63%) and a low recurrence rate (15%), as sclerosing agent [27]. Zulfiqar et al (1999) confirmed it safety and effectiveness, especially when dealing with macro-cystic lesions [28]; a decade later, Sanldas et al (2011) confirmed a higher success when treating unilocular malformations [29]. Analogous outcomes, along with similar success rates, were obtained by Kurmar (2012) [30], Jain (2013) [31], Porwal (2018) [32] and Hashmi (2020) [33]. Orford et al (1995), obtained minimal surgical scars and declared a low risk of potential injury of nerves and/or blood vessels. Local signs of inflammation (restricted movement of the neck, pain, swelling, induration, stridor, difficulty in breathing or swallowing, intra-luminal bleed, infections) subside spontaneously within few days. Systemic effects range from mild (vomiting, diarrhoea. flu, local hyperpigmentation, hyperkeratosis and thickening of the skin) to anaphylaxis [34]. Mathur et al (2005) declared no major complication or mortality [35]; the same conclusion was drawn by Rozman (2010) [22]. Sporadic cases of pulmonary fibrosis actually occur only when high doses are employed (total administration of 400 U or single administration of 30 mg/mm^2), as during systemic chemotherapy or with renal clearance under 25-35 mL/min. Follow-up to monitor for pulmonary fibrosis is left to exercise tolerance and patients are also advised to avoid live vaccine for 3 months. The suggested dose is between 0,5 and 1 mg/kg with a maximum of 5 mg/kg [35].

Pingyangmycin or bleomycin A5 *(table 4)* is similar to common bleomycin (A2) but it is cheaper and determines less peri-lesional fibrosis and complications, with possible hair loss, gastrointestinal reactions, fever, rash. The recommended dose is 1 mL/cm^2 and must be lower than 8 mg per single injection and 40 mg in total. Jia et al. (2014) treated orbital and peri-orbital lymphatic malformations with PYM, with a mean volume decrease of 84% after a median number of 2 injections, and no recurrences at 8 months were observed [12]. Gao (2002) employed it also with oral, maxillofacial and cervical lesions, considering it as a potential primary therapy [14].

Doxycycline *(table 3)* is a bacteriostatic antibiotic, which inhibits angiogenesis through the blockage of the production of metalloproteinases and vascular endothelial growth factor (VEGF) [10]. It is inexpensive, widely available and it has minimal side effects, including dental discolouration in children, allergic reactions [2], haemolytic anaemia, hypoglycaemia, neurological complications and rare cases of methaemoglobinaemia [36]. Pain, swelling, haemorrhage and cellulitis may occur, as well as scarring, skin excoriation and Horner's syndrome [2]. Complete or near complete response was achieved from the very beginning of its use, as reported from the experience of Cordes (2007) [37] and Nehra (2008) [38]. Later, Jeffrey Cheng (2015) performed sclerotherapy with doxycycline on a larger cohort of subjects, reporting an efficacy of 84.2%, and insufficient responses or recurrences in 33% [2]. The recommended dose varies between 20 and 150 mg at a concentration of 10 to 20 mg/mL [36]. Despite many Authors, such as Cahill (2011) [39] and Farnoosh (2015) [36], state its primary role for the treatment of large macro-cystic malformations, some others like Burrows (2008) declare an even higher efficacy than OK-432 in case of micro-cystic lesions [11]. Shields (2009) agreed with the former and employed it also in cases of post-surgical recurrences [40]. Shergill (2012) put together the theories from the previous authors claiming that doxycycline could be used for nearly all types (macro-cystic, micro-cystic or mixed) of lymphangiomas [41].

Despite the few quotations, sodium tetradactyl-sulphate or sotradecol 3% *(table 4)* is used in many paediatric centres in the UK as second like after doxycycline. It has shown to determine an average response of 80-90% (complete in 40%) and complication rate of 17% only, including swelling, oedema, mild allergic reaction, chronic facial pain, infections, cutaneous necrosis and nerve injury. Dose varies between 3 to 6 mL and its main indication remains orbital LM [25]. Farnoosh (2015) achieved similar results, with an even better outcome if combined with doxycycline [36].

Alcohol 98% *(table 4),* used for many arteriovenous malformations, causes rapid cellular dehydration and protoplasm precipitation. On one hand, it shows good therapeutic response (from 64 to 96%), large availability and low cost. On the other hand, it can determine unexpected damage within the surrounding tissues and, at high doses, severe systemic effects such as hypotension, respiratory depression, arrhythmias, seizures, hypoglycaemia and exitus. For this reason, low doses are employed (0,5-1 mL/kg), mostly associated with injuries of skin, mucosae and peripheral nerves

(7,5-27,95%) or thrombotic phenomena. Recurrence rate is around 30% [6]. Impellizzeri et al. (2010) reported their experience with CT-guided instillation of 5-15 mL of alcoholic solution with complete disappearance of the lesion in 7 patients, with only one needing a second injection. Only one patient experienced self-limiting erythema and tenderness and no recurrence was observed at 2 years [1]. Puig et al. affirmed that the use of ethanol for lymphatic malformations could cause the extravasation as a major risk. To avoid it, he proposed a double-needle procedure to limit the total volume of ethanol injected in order to reduce intra-lesional pressure and thus extravasation [42]. Ethanolamine oleate is obtained from a combination of an organic base with oleic acid and shows alcohol-like effect, although it has lower toxicity [12].

Although few experiences about the use of acetic acid at 30-50% *(table 4)* demonstrate a more rapid effect compared with the other SA and the frequent need for a single treatment session only, the extravasation into the nearby tissues represents a serious issue. As an example by Won et al, a patient with a cervico-mediastinal lymphangiomas experienced infiltration in the lung parenchyma surrounding the lesion [43].

Alcoholic solution of Zein (Ethibloc, *table 4)* contains Zein (a prolammine), diatrizoate sodium (radio-opaque marker), poppyseed oil and 96% ethanol. It is biodegradable, effective and safe, but the risk of scars, salivary fistulas, infections and the poor aesthetic results (30 days of trans-cutaneous elimination) have limited its use. The recommended dose is between 1 and 7,5 mL. M. A. Emran et al. reported satisfactory to excellent results in 84% of macro-cystic/mixed and in 77% of micro-cystic lesions and considered Ethibloc an effective alternative to surgery for macro-cystic lymphangiomas or post-surgical recurrences. Failure and subsequent recurrence rate seems around 23% [44].

Fibrin glue (Tissucol, *table 4*) is an expensive haemostatic agent making the cysts collapse, the dose being 10 to 15% of the suctioned volume; Castañon et al obtained complete remission of 8 of 9 monocystic neck lymphangiomas [45]. Polidocanol *(table 4)*, a local anaesthetic, is administered at the dose of 1 mL for each cm of lesion, does not need further anaesthesia and causes erythema with induration of the skin only; Jain et al achieved a volume reduction of 96% to 100% in 3 patients [46].

To the knowledge, some substances are administered orally in addition to local treatments and overseen by a physician in normal circumstances. Sirolimus or rapamycin is a mTOR-PI3K pathway inhibitor increasingly employed when surgery fails or is not feasible. It has been used for orbital lymphatic malformations and (later) conjunctival or superficial peri-ocular lesions [12, 47]. Other systemic treatments include Cyclophosphamide (alkylating antineoplastic agent), interferon, steroids (promoting inflammation and cicatrisation respectively), isotretinoin, Bevacizumab, Thalidomide (anti-angiogenic), Alpelisib and TIE2 (targeted therapy against PIK3CA and tunica intima endothelial kinase 2), propranolol and sildenafil (relaxing smooth muscle thus causing cystic decompression and opening of secondary lymphatic spaces). The last one, a phosphodiesterase type 5 inhibitor used for erectile dysfunction and pulmonary hypertension, proved effective in reducing the number and severity of bleeding episodes, especially with macro-cystic and mixed lesions [12]. Newest target-therapies, appearing more effective with macro-cystic lesions, include PI3K inhibitors (LY294002, BYL719, wortmannin), AKT inhibitors (ARQ092, MK-2206), MAPK inhibitors, (U0126), multiple kinase inhibitors (sorafenib, trametinib), VEGF-A inhibitors (bevacizumab), BMP and Wnt modulators (dorsomorphin, LDN-193189 and calyculin A), JAK inhibitors (ruxolitinib), calcium channel blockers (amlodipine), KATP activators (minoxidil), zoledronic acid, interferon a 2b, prednisolone, sunitinib. However, large-scale studies are required in order to confirm efficacy and potential side-effects for each substance [10].

A recent review by Liu et al. (2021) confirms how, although surgery remains the first-line strategy for lymphangiomas (especially large lesions for possible complete removal), risk of scars, incomplete resection/recurrences and injury to blood vessels or cranial nerves (especially the submandibular branch of the facial nerve) is high. Thus, despite above-mentioned side effects like soft-tissue oedema and skin necrosis as well as variable recurrence rates, sclerotherapy may often represent the elective treatment; moreover, micro-cystic lesions appear more and more susceptible to SA like OK-432. However, since “single treatments” often achieve insufficient results, ongoing strategies tend to administer multiple therapies. For example, surgery may obtain debulking of large lesions, with remaining tissue being treated with sclerotherapy (e.g. bleomycin) and systemic drugs administered to alleviate the symptoms of pain and bleeding. Analogous strategies might be employed with superficial micro-cystic mucosal lesions, where RFA or laser-therapy plays the main role. Moreover, oral medications themselves may be used prior to surgery and/or sclerotherapy. However, further studies are necessary in order to promote univocal guidelines; thus, to date, as already stated by Liu et al., “individual therapies” (also including target-therapy) represent the most appropriate strategy in the treatment of lymphangiomas, with no exception for cervical lesions [10].

V. Conclusion

Treatment of cervical lymphangiomas represents a rare but challenging issue. Despite the wide range of treatments discussed, cervical lymphangiomas remains a relatively infrequent finding. Thus, a limited number of studies is reported in literature and small cohorts of patients are considered, with subsequent difficulties in performing a reliable meta-analysis about the efficacy of any single treatment.

Despite the lack of worldwide-accepted guidelines, our research highlights the role of sclerotherapy as the first-line non-surgical strategy because of the lower rates of aesthetic sequelae, recurrence, complications (e.g. injury to blood vessels or cranial nerves) and mortality and the better course, so that it might represent a valid or equivalent alternative to surgical therapy. Moreover, the two treatments can be used in combination (e.g. when remaining lymphangiomatous or fibrous tissue is present) or sclerotherapy can prove more efficient (e.g. micro-cystic lesions when using OK-432). Sclerosing agents should usually be employed with macro-cystic lesions, and no substantial difference is reported in terms of efficacy from a SA to another, all of them ranging from about 60 to 90% in different studies. Although no longer used in several countries (including the UK), OK-432 would be optimal for its minimal extravasation (and thus peri-lesional fibrosis and aesthetic sequelae), the lowest rate of both local and systemic complications and recurrences (around 10%) and, eventually, the feasibility with either micro-cystic lesions. Bleomycin can represent a valid option as long as low doses are administered, due to the well-known risk of pulmonary fibrosis; the issue is partially solved when employing pingyangmycin which is still, however, indicated mostly for peri-ocular lesions. Doxycycline is more available, cheap and apparently even more efficient than OK-432 in cases of micro-cystic lymphangiomas; as an alternative, we suggest tetradactyl-sulphate. Despite its wide availability and low cost, the higher risks of neurovascular/visceral injuries (about 10 to 30%), systemic side effects and recurrences (around 30%) make ethanol a definitely second-line treatment.

However, several considerations must be made. Firstly, multicentric prospective studies are necessary in order to better evaluate this technique and define the best sclerosing agent to be used. Secondly, as already mentioned, ongoing strategies tend to combine the above-mentioned treatments (including oral medications and the newest “target-therapies”) according to each patient’s characteristics and lesions (as well as psychological aspects), giving rise to a multi-faceted approach.

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All authors contributed to the study conception and design, read and approved the final manuscript.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Consent for publication was obtained for every individual person’s data included in the study.

The authors affirm that human research participants provided informed consent for publication of the images.

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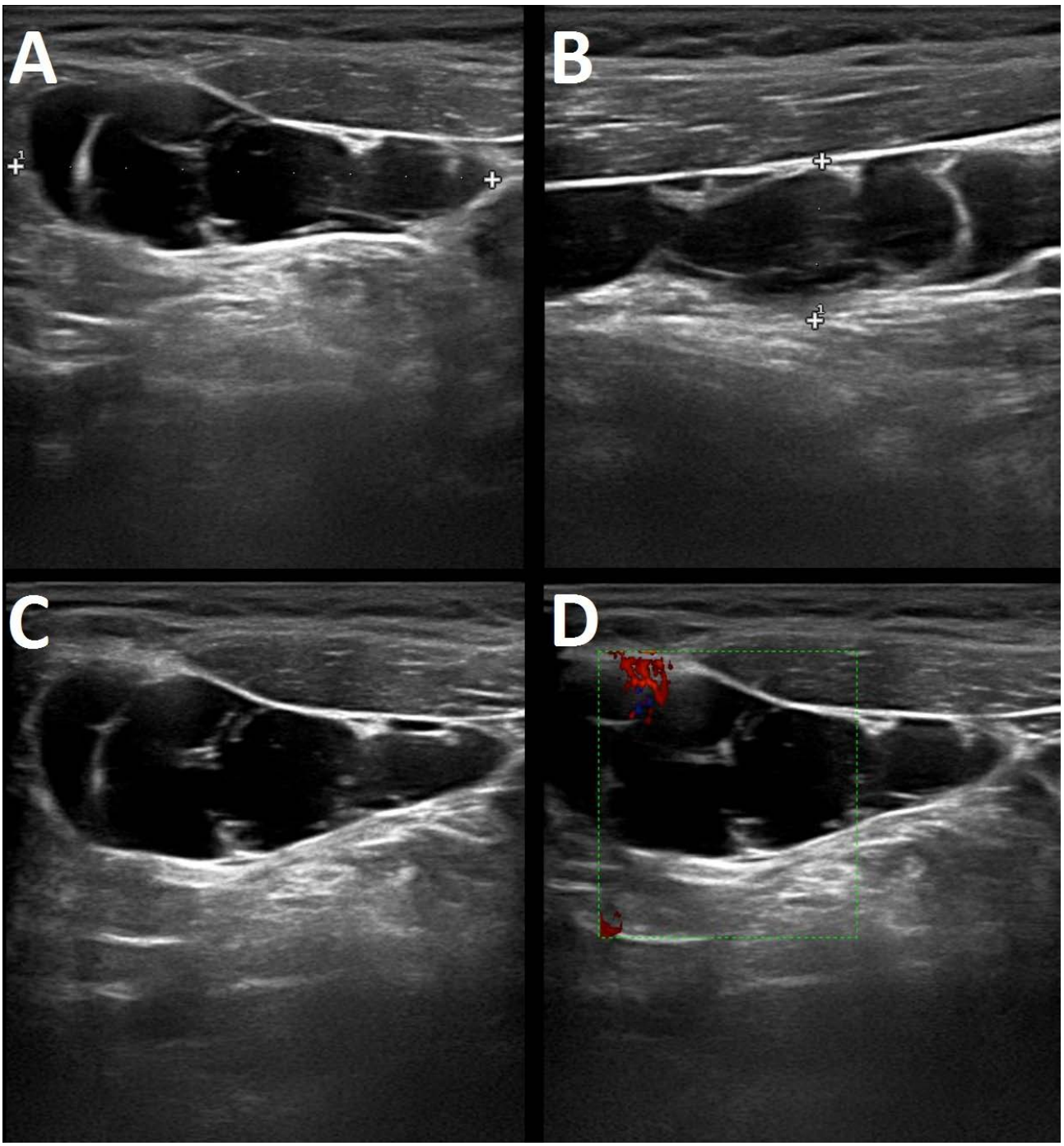
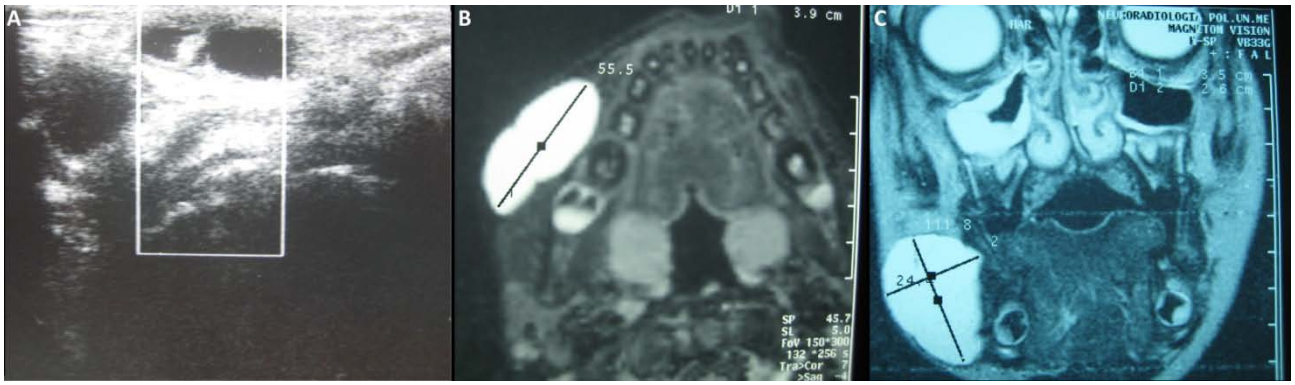


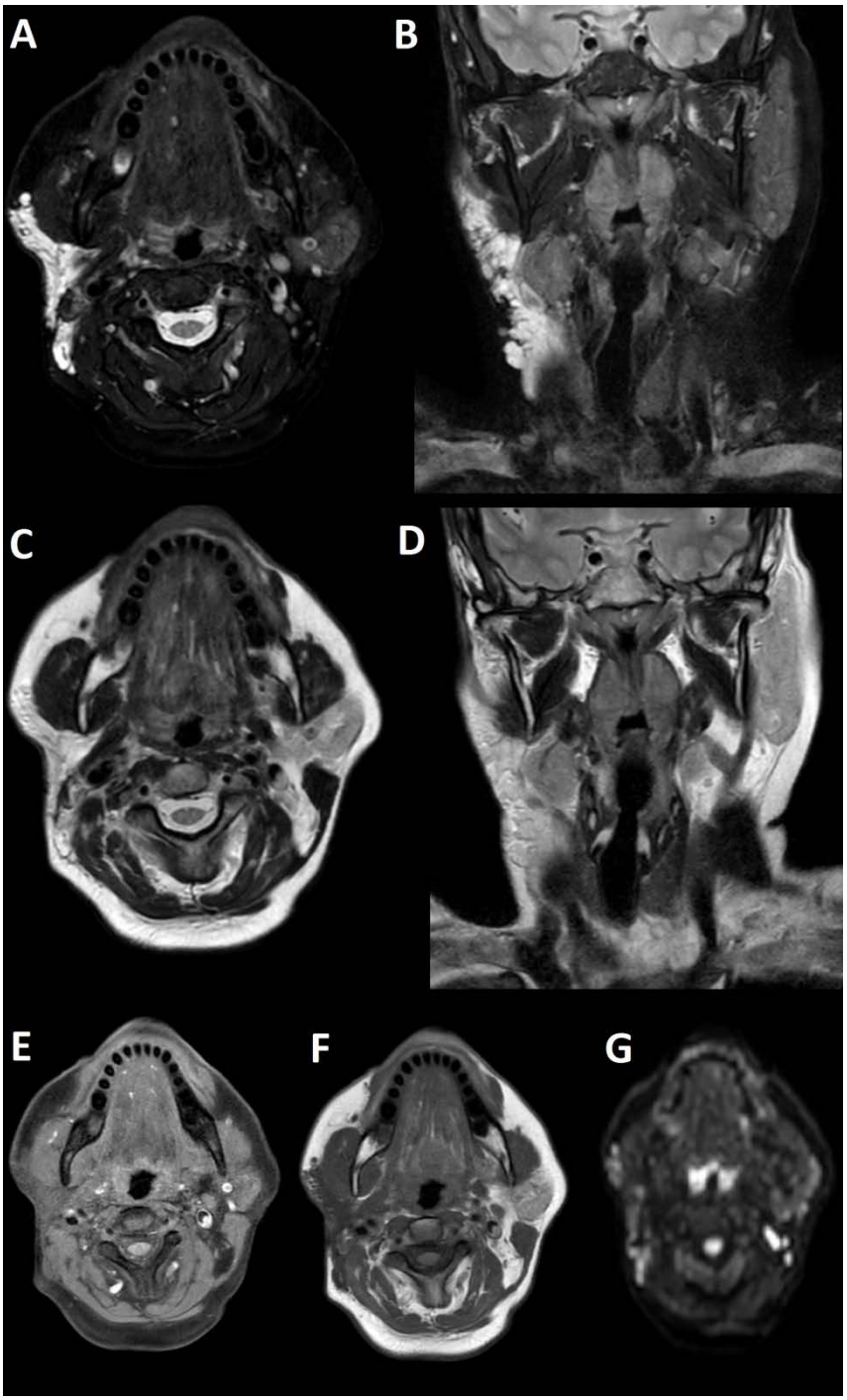
Figure/Patient 1

A 7 year-old girl presenting with a tumefaction at the level of the right latero-cervical region. US scans show a 43x14 mm subcutaneous fluid formation with septa extending from the root of the neck to the submandibular region (**A-B**). Doppler-mode demonstrates lack of blood flow within the lesion or the septa (**C-D**). Diagnosis of cystic lymphangioma is done.



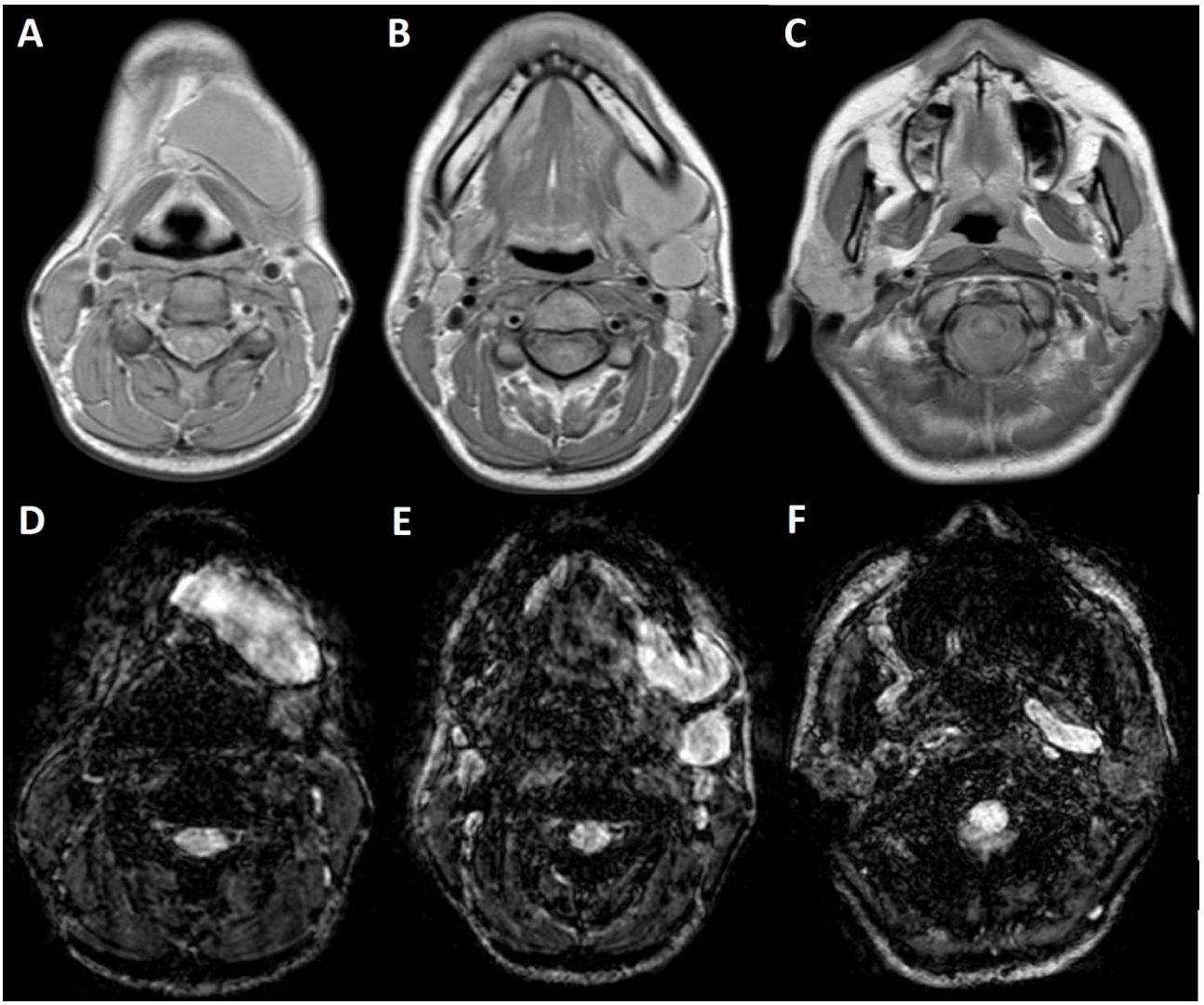
Figure/Patient 2

A case of right mandibular lymphangioma in a 10 year-old boy, hypoechoic with some septations and no blood vessels (**A**) and hyper-intense on T2 axial (**B**) and coronal (**C**) MR scans.



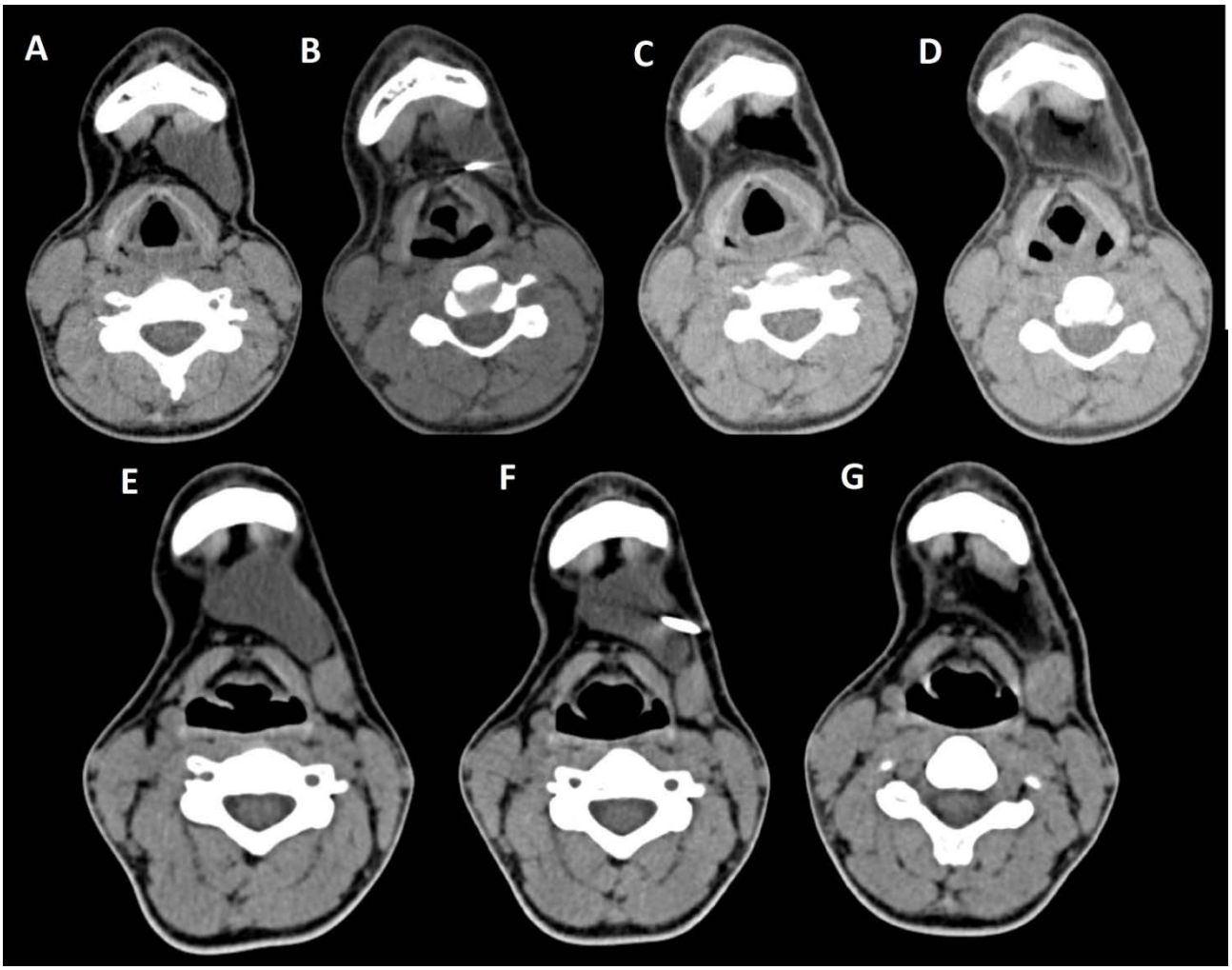
Figure/Patient 3

An 8 year-old girl with prior surgical excision of a right latero-cervical lymphangioma presenting with a new-onset tumefaction within the same region. MRI scans show a 9-10 cm subcutaneous multilocular lesion, extending between two virtual planes crossing the retro-molar trigone and the thyroid respectively, with deep invasion of para-pharyngeal spaces cranially and the space between the submandibular gland and the vascular peduncle of the neck caudally. The lesion appears hyper-intense on T2 weighted scans with (A-B) and without (C-D) fat suppression, hypo-intense on T1 weighted scans with (E) and without (F) fat suppression and hyper-intense on DWI scans with high B values (G). Diagnosis of loco-regional recurrence of cystic lymphangioma is done.

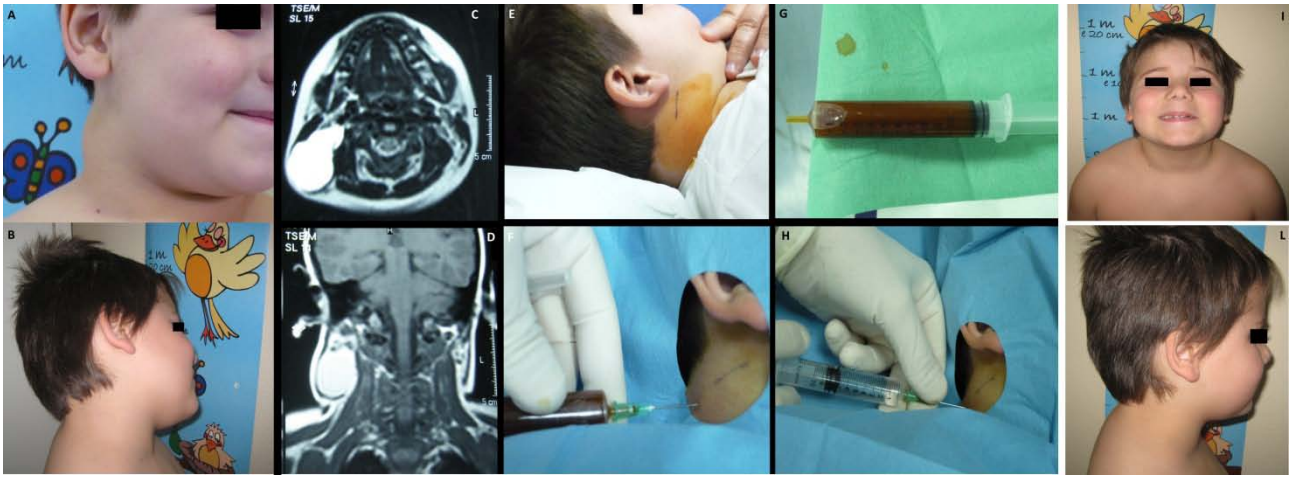


Figure/Patient 4

1. A 7 year-old girl presenting with a tumefaction at the level of the left latero-cervical region. MRI scans show a subcutaneous lesion occupying the left submandibular, parotideal, para-pharyngeal and part of the masticatory spaces. The lesion appears slightly hyper-intense on T1 (**A-C**) and markedly hyper-intense on T2 (**D-F**) scans. Diagnosis of cystic lymphangioma is done.

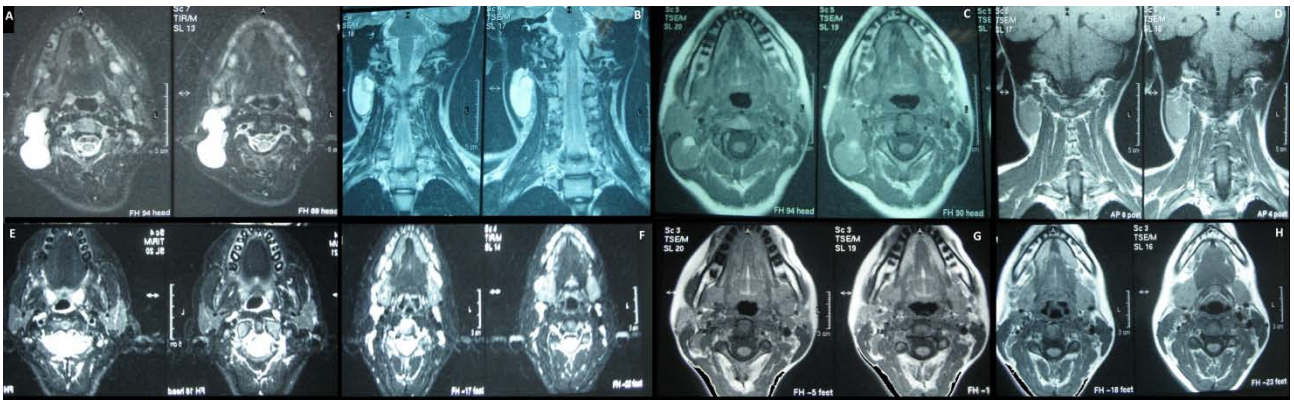


2. The same patient undergoing two different sessions (A-D and E-G, respectively) of sclerotherapy with absolute ethanol. An 18-G needle is introduced into the lesion and about 10 cc of citrine-turbid fluid are aspirated (B and F). Then, 5 cc of ethanol are injected and the patient is mobilised in order to distribute the SA throughout the lesion (D and G). The patient is dismissed and a one-week antibiotic therapy is prescribed.



Figure/Patient 5

A 6 year-old boy presenting with a right latero-cervical tumefaction (**A-B**): axial (**C**) and coronal (**D**) MR scans show an expansive subcutaneous formation with high T2-signal, consistent with lymphangioma. The patient is demanded for sclerotherapy with ethanol: after disinfection and sterilisation of the skin (**E**), a fine needle is introduced into the lesion (**F**) and a yellowish viscous fluid is aspirated (**G**); then, alcohol is injected into the lesion (**H**). No recurrence is visible at two months-follow up (**I-L**).



Figure/Patient 6

Another case of a right latero-cervical lymphangioma in a 8 year-old boy, markedly hyper-intense on T2 axial (**A**) and coronal scans (**B**) and slightly hyper-intense on T1 axial (**C**) and coronal (**D**) MR scans. The patient is demanded for sclerotherapy with ethanol: no recurrence is visible at the follow-up MR T2 (**E-F**) and T1 scans (**G-H**).

Table 1: Data from literature about OK-432

	Advantages	Success rate	Recurrence rate	Complications	Dose
Ogita S. et al (1987) [13]	Low toxicity, immuno-stimulating effect	89% (total: 9 patients)	11%	Local inflammation, fever	As much as aspired by mixing each 0.1 mg with 10 cc distilled water, not exceeding 0.2 mg on total; next injection at 3-4 week
Luzzatto G. et al (2000) [17]	effective for primitive, residual and recurrent lesions, low invasivity and scarring	Excellent results in macrocystic, good and poor in 25% and 75% of mixed type (total: 11 and patients respectively	9.1%	Fever, signs of local inflammation, cervical swelling needing a feeding tube	0.1-0.2 mg/dose (one to 16, average 3)

Ruiz E. et al (2004) [23]	significant volume reduction also in microcystic lesions, feasible when there is risk of airway obstruction	complete remission in 63% (prevalently macrocystic), partial response (50 to 70%) in 27% (prevalently mixed); (total: 19 patients)	None	Fever, erythema, oedema, infection	(see Ogita) One to eight administrations
Sichel et al (2004) [18]	No perilesional fibrosis	complete or sub complete resolution in 73%, no response in 27% (total: 11 patients)	9.1%	Local inflammation, fever, odynophagia	0.01 mg/mL of the lesion's fluid, with a maximum of 0.2 mg in the first injection and 0.3 mg in the second or third injections
Yoo et al (2009) [20]	only minor complications, high long-term efficacy	Short term (83.5%) and long-term (76.3%), varying from macrocystic (92%) to microcystic (62%), from unilocular (94%) to multilocular (64%), from below (77.8%) to above mylohyoid muscle (21.7%) or mixed (20.3%); (total: 55 patients)	42% after first administration, lower in the next	Neck discomfort, swallowing difficulty, disfigurement of face, dyspnoea	(see Ogita) One to five administrations
Rebuffini E. et al (2012) [21]	No perilesional fibrosis, good response to additional treatments	Complete remission in 53.33%, marked reduction in 33.33%, moderate response in 13.33% (total: 15 patients)	12.5%	pain, redness, induration, fever, anaemia, transitory increase of platelets' concentration	0.2 mg per session (one to three), each separated by 6 months
Efe N. et al (2016) [15]	Minimal extravasation and damage of nearby tissues, does not preclude further surgery	66% for microcystic lesions, almost 100% for macrocystic lesions	12%	Local pain, heat, oedema, anaemia and rare penicillin allergies	(see Ogita)
Hazim et al (2016) [16]	Minimally invasive, little scar, does not interfere with subsequent surgery	Complete remission in 16.66%, marked reduction in 50%, mild reduction in 16.66% and no response in in 16.66% (total: 6 patients)	None within responding lesions	Fever	0.01 mg/m in one to eight administrations

Table 2: Data from literature about Bleomycin

	Advantages	Success rate	Recurrence Rate	Complications	Dose
Tanigawa et al (1987) [25]	Less recurrences when compared with surgery, feasible after surgery failure	excellent results in 53%, good results in 47% (total: 15 patients)	none	Swelling, fever, vomiting, diarrhoea, local infection, dyspnoea	0.3 to 0.5 ml, once every 4 to 6 weeks, microsphere in-oil emulsion
Sung et al (1995) [26]	feasible with unresectable lesions (debulking)	complete or nearly complete shrinkage 40%, marked reduction in size in 30%, partial or minimal reduction in 30% (total: 10 patients)	None within responding lesions	local swelling and inflammation, pneumonia of uncertain origin	1 mg/mL, from 3 to 7 sessions
Orford et al (1995) [34]	low risk of neurovascular damage, no surgical scar	excellent results in 45%, good in 36%, no response in 18% (total: 11 patients)	9%	fever, vomiting, cellulitis, skin discoloration	0.3 to 0.6 mg/kg
Zulfiqar et al (1999) [28]	Safe and effective, especially in macrocystic lesions	excellent results in 36%, good in 45%, no response in 18% (total: 11 patients)	None in short-term	none	0.5 mg/kg from 1 to 4 sessions
Mathur et al (2005) [35]	no major complications, no mortality	complete or near complete response in 30%, good response in 70% (total: 10 patients)	30% (70% residual disease)	local swelling and inflammation	1 mg/kg with a maximum of 6 mg/kg, every 2 weeks, in a solution of 1 mg/ml in large lesions and 2 mg/ml in smaller lesions.
Rozman et at (2010) [22]	Safe and effective, no major complication when using normal doses	Complete resolution in 63%, good response in 21% and poor response in 16% (total: 22 patients)	8%	Swelling, stridor, difficulty in breathing or swallowing, pain, tenderness, erythema	0.5 mg/kg with a maximum of 5 mg/kg, from one to six sessions
Sandlas et al (2011) [29]	Safe and effective with unilocular lymphatic malformations	significant response in 53.33%, good response in 33.33% poor response in 13.33% (total: 15 patients)	None within responding lesions	fever, swelling, skin discoloration	0.6 to 0.8 mg/kg
Kumar et al (2012) [30]	Safe and effective	excellent response in 20%, good in 74.29%, poor in 5.71% (total: 35 patients)	None within responding lesions	fever, transient increase in size of swelling, local infection, intraluminal bleed, skin discoloration	0.5 mg/kg body weight, no more than 10 units at a time

Jain et al (2013) [31]	Safe and effective with macrocystic	Complete response in 100% (total: 8 patients)	None in short-term	Fever, erythema	0.6 mg/kg, from one to three sessions
Porwal et al (2018) [32]	Safe and effective with macrocystic lesions, no major complications	Complete resolution in 62.5%, good response in 25%, poor response in 12.5% (total: 8 patients)	None within responding lesions	Fever, erythema, pain , restricted movement of the neck, abscess	0.5 mg/kg, from one to three sessions
Hashmi S et at (2020) [33]	Safe and effective, especially with macrocystic lesions	Excellent results in 20%, good results in 72.5%, poor results in 7.5% (total: 31 patients)	None within responding lesions	Post-procedural swelling, fever, local tenderness, skin changes	0.3 IU/kg, from one to three sessions

Table 3: Data from literature about doxyclicline

	Advantages	Success rate	Recurrence Rate	Complications	Dose
Cordes et al (2007) [37]	readily available, inexpensive	Resolved or marked reduction in all patients (total: 12 patients)	None within responding lesions	Swelling, haemorrhage into the cystic cavity	10 mg/mL
Nehra et al (2008) [38]	readily available, inexpensive	Complete response in macrocystic lesions, partial response in mixed lesions (total: 11 patients)	18%	None	10-mg/mL up to a maximum of 200 mg
Burrows et al (2008) [11]	Effective, safe, few complications	Excellent response in macrocystic (90%), good in combined (80%) and in microcystic (60%) lesions (total: 41 patients)	None within responding lesions	pain and swelling, skin blisters, hair loss, Horner's syndrome	10 mg/mg, with a maximum dose of 1000 mg or 20 mg/kg, from 1 to 6 administrations
Shiels et al (2009) [40]	Feasible for primary lesions (even microcystic) or post-surgical recurrences	Excellent response in 90% (total: 17 patients)	13%	Cellulitis, haemorrhage into cysts	20 mg/mL, one to four sessions
Cahill et al (2011) [39]	Feasible for large macrocystic head and neck lymphatic malformations	Excellent response in 65%, good in 23%, poor in 12% (total: 17 patients)	None within responding lesions	emolytic anaemia in 2 infants, hypoglycaemic and metabolic acidosis, transient hypotension, skin excoriation, delayed neural complications, Horner's syndrome, transient left lip weakness, right facial nerve palsy and left hemidiaphragm paralysis	10 mg/mL with a dose range of 50 to 500 mg

Shergill et al (2012) [41]	Safe and effective with all types of lesions	Excellent or satisfactory response in 90% (total: 14 patients)	None within responding lesions at short-term	respiratory distress, pain, swelling, cosmetic deformity, leakage from the skin, Horner's syndrome	10mg/mL with a maximum of 300 mg in patients under 12 and 1200 mg in patients over 12
Cheng (2015) [2]	inexpensive, widely available, minimal side effects	84.2% with 60.5% after the first session (total: 38 patients)	Not available (patients lost to follow-up)	Tooth discoloration, allergic reactions, haemorrhage into cysts, cellulitis, pain, increased swelling, scarring, skin excoriation, Horner's syndrome	10mg/mL with a maximum of 20mg/mL
Farnoosh et al (2015) [36]	Safe and effective, especially with macrocystic and mixed lesions	complete resolution in 50%, satisfactory improvement in 25%, poor response in 25% (total: 29 patients)	None within responding lesions	infection, exacerbation of the lesion, jaw pain, facial swelling	10 mg/ml, ranging from 20 to 150

Table 4: Data from literature about other sclerosing agents

	Advantages	Success rate	Recurrence rate	Complications	Dose
Pingyangmicin (Jia et al, 2014) [12]	feasible for orbital or periorbital malformations	marked improvement in 76%, moderate in 18% (total: 33 patients)	none within responding patients	swelling of the conjunctiva, localized subcutaneous atrophy	1 mL/cm^2, be lower than 8 mg per single injection and 40 mg in total
Pingyangmicin (Gao et al, 2002) [14]	could be the primary therapy for oral, maxillofacial and cervical lesions	curative in 100% of cystic, 46.36% of capillary, 16.16% of cavernous and 19.05% of mixed capillary and cavernous lesions (total: 195 patients)	none within responding patients	mild and local	5 mg to 70 mg and 5 to 58 times, 1 time per 2-4 weeks
Alcohol 98% (Impellizzeri et al, 2010) [1]	large availability and low cost	100% (total: 8 patients)	none at 2 years	erythema and tenderness (if high doses are employed: hypotension, respiratory depression, arrhythmias, seizures, hypoglycaemia, exitus)	5-15 mL of solution, each but one needing one session only

Sodium tetradecyl-sulphate (Farnoosh et al, 2015) [36]	feasible for orbital lesions	complete resolution in 60%, satisfactory to poor response in 40% (total: 29 patients)	none within responding patients	tongue swelling, bleeding, difficulty chewing, oedema, mild allergic reaction, chronic facial pain, infections, cutaneous necrosis, nerve injury	3 to 6 mL
Acetic Acid (Won et al, 2004) [43]	Effective, no serious complications (if no systemic absorption occurs)	Complete resolution in 60%, good resolution in 40% (total: 5 patients)	none	pain	2 to 5 mL
Ethibloc (Emran et al, 2006) [44]	Safe, effective and biodegradable	satisfactory to excellent results in 84% of macrocystic/mixed and in 77% of microcystic lesions (total: 35 patients)	none within responding patients	scars, salivary fistulas, infections, aesthetic sequelae	1 to 7,5 mL
Tissucol (Castanon et al, 1999) [45]	Excellent long-term results and few complications	Remission in 89% (total: 9 patients)	11%	none	10% to 15% of the suctioned volume
Polidocanol (Jain et al, 2002) [46]	Safe, painless, effective	Remission in 100% (total: 3 patients)	none	superficial erythema, induration of the skin	1 to 6 mL, in 1 to 20 injections

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Magnetic Resonance Imaging in Evaluation of Avascular Necrosis of Femur

By Varigonda Mahidhar, Dr. Ram Krishna N & Dr. Jyotsna Rani. Y
Nizams Institute of Medical Sciences

Abstract- *Objectives:*

1. To assess the role of MRI in the diagnosis and staging of Avascular necrosis of the femoral head.
2. To evaluate the demographic profile with emphasis on risk factors for AVN.
3. To evaluate the most common quadrant of the femoral head affected in AVN.
4. To analyze the MRI findings in AVN of the femoral head.

Methods: This single-center retrospective observational study was conducted in the department of radiodiagnosis in a tertiary care institute situated in an urban area. 70 patients of all age groups with clinical suspicion of AVN were evaluated over a period of one and a half years between January 2020 to June 2021. Of these, 6 patients with osteoarthritis were excluded with 64 patients included in this study. Demographic and clinical details with particular emphasis on risk factors and relevant lab parameters were collected from records and reviewed for all patients. Scans were performed on 3-Tesla MRI scanner, Seimens SkyraTM. Ficat and Arlet classification was used to stage the disease.

GJMR-D Classification: *DDC Code: 363.700973 LCC Code: GE150*

Strictly as per the compliance and regulations of:

Magnetic Resonance Imaging in Evaluation of Avascular Necrosis of Femur

Varigonda Mahidhar [α], Dr. Ram Krishna N [σ] & Dr. Jyotsna Rani. Y [ρ]

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Results: In this study of 64 patients, 70% were males and 30% were females. Bilateral disease was found in 83% patients and unilateral involvement in 17% patients. The associated risk factors of AVN in our study were alcohol(36%), steroids(27%), idiopathic(19%), sickle cell disease, SLE, trauma, diabetes. Of the 117 femoral heads affected, stage I AVN was found in 1 femoral head, stage II in 45 heads, stage III in 50 whereas stage IV in 21 femoral heads. Anterosuperior quadrant was involved in 62% of the femoral heads.

Conclusion: Our study demonstrates that MRI is the imaging of choice in clinically suspected cases of AVN and in proper staging. It helps in early diagnosis and better outcome.

I. Introduction

Avascular necrosis(AVN) is the cellular death of the bone due to various factors causing vascular compromise. This vascular compromise leads to ischemia and cell death which will result in relentless progression of the disease. Femoral head is the most commonly affected site as it is the weight bearing part of the bone and due to its precarious bloodsupply.AVN of the femur is one of the common causes of hip pain presenting in young age. Some of the common risk factors associated with AVN include trauma, corticosteroid use, chronic alcoholism, pancreatitis, sickle cell disease, gout, radiation, SLE(1,2).

Radiologic staging of the disease is of crucial importance in the identification and risk stratification in pre-collapse stages, prognosis, treatment planning, and post-operative follow-up. Radiograph of the pelvis with both hips is the first imaging usually done in a suspected case of AVN, but unfortunately, plain radiographs are of no much use in early stages of AVN(3). MRI is the most sensitive imaging modality in diagnosing AVN. It is the investigation of choice for the definitive staging of AVN, because images clearly portray the size of the lesion, and overall estimates of the stage of disease can be made. CT is usually done to assess the extent of disease and to look for subchondral fractures or collapse.(4) SPECT scanning has a role in determining the radioactivity of the organ and it is beneficial in early cases to spot the avascular focus that can be un noticed with routine plain MRI sequences. Bone scanning is advised in cases where MRI is contraindicated or equivocal, and it is useful in quantifying the physiologic data i.e., uptake in static and perfusion states. Bone biopsy is accurate, and can diagnose early, however, usually avoided as it is invasive(7).

II. Materials and Methods

This single-center retrospective observational study was conducted in the department of radiodiagnosis in a tertiary care institute situated in an urban area. 70 patients of all age groups with clinical suspicion of AVN were evaluated over a period of one and a half years between January 2020 to June 2021. Of these, 6 patients with features of osteoarthritis were excluded. Demographic details like age, gender and clinical symptoms were collected. Clinical details with particular emphasis on the risk factors for AVN and relevant lab parameters were collected from records and reviewed for all patients. Scans were performed on 3 Tesla MRI scanner, Siemen's SkyraTM. Ficat and Arlet classification was used to stage the avascular necrosis of the femoral head.

III. Results

In this study of 64 patients with osteonecrosis of femoral head, 41(69%) were males and 18 (31%)were females with male to female ratio of 2.2:1.

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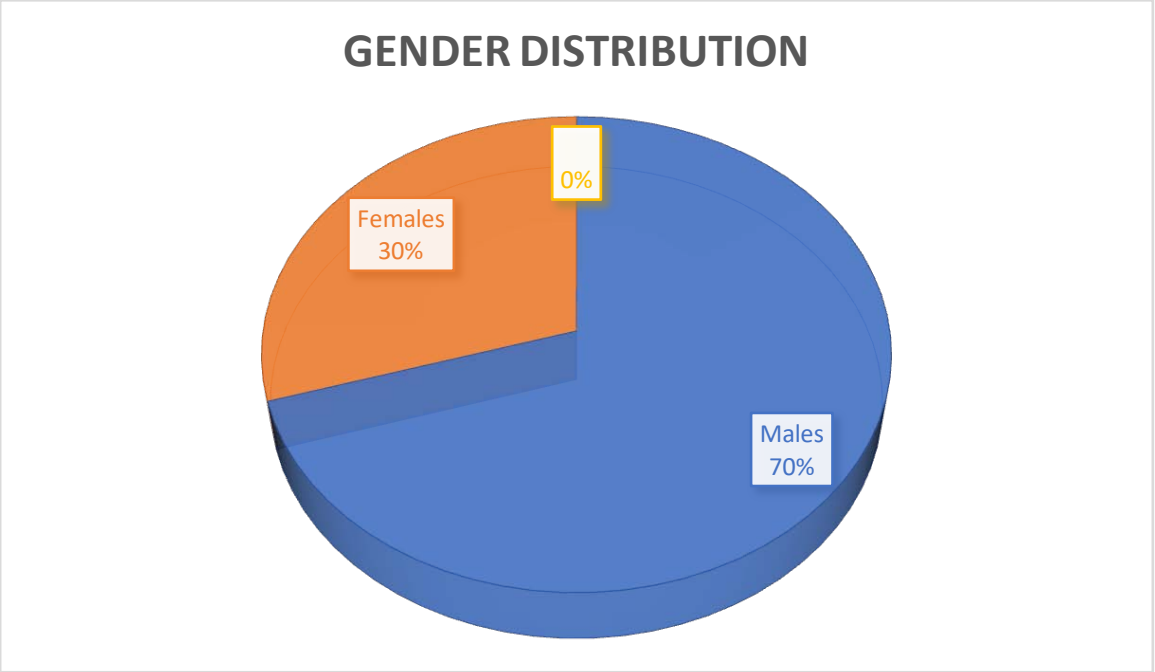
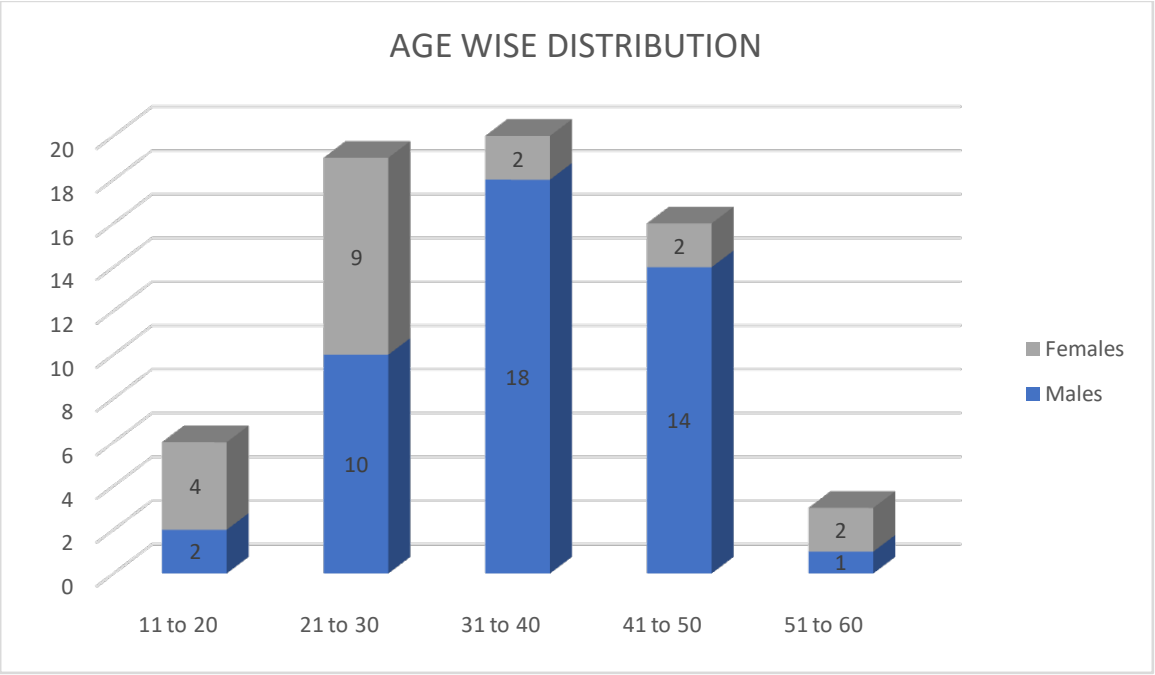
Author ρ: Professor & Head, Department of Radiology and Imageology, Nizams institute of medical sciences, Hyderabad, India.



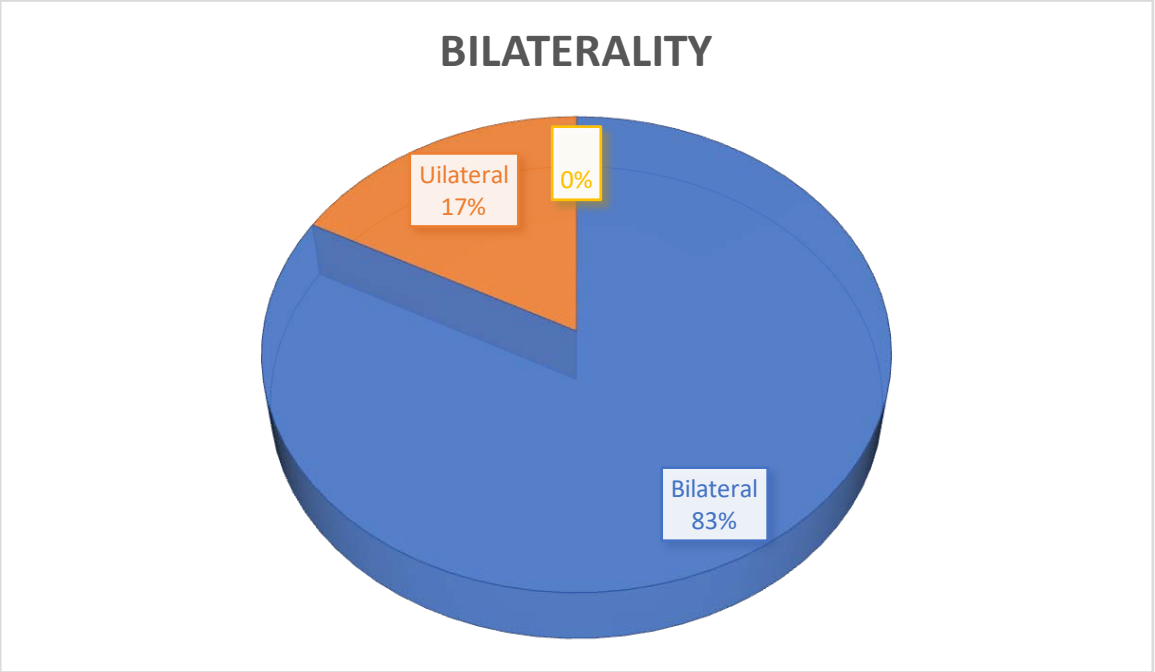
Graph 1: Gender distribution of the cases

Prevalence of AVN was found to be highest in the economically productive age group of 21 to 40 years (62.7%) i.e 37 cases, 5(8.4%) cases belongs to age group of 11-20 years,14 (23.7%) cases belongs to the age group of 41-50 years and 3(5%) cases belongs to the age group of 51-60 years. The mean age of presentation was found to be 33.98+/-10.03. There is no statistical significance between the mean ages of presentation in males and females (M=35.05,F=30.67).



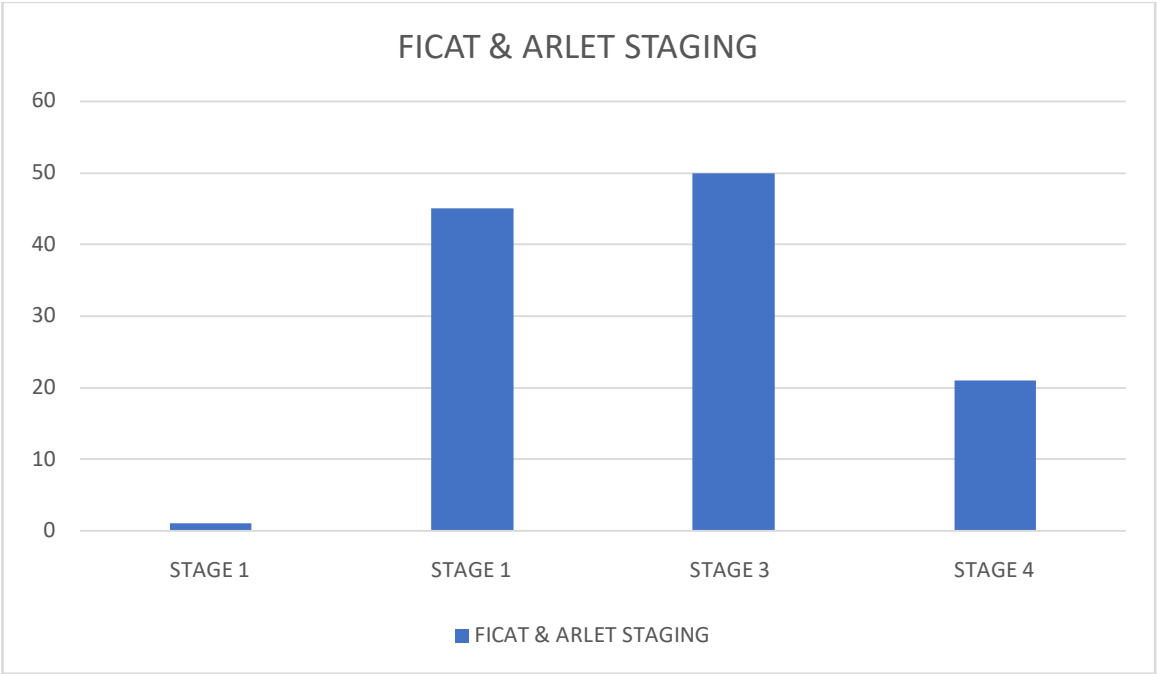
Graph 2: Age wise distribution of cases.

In the present study, The presentation was bilateral in 48(81.3%) and unilateral in 11(18.6%) cases.



Graph 3: Chart showing the side affected.

We detected stage I AVN of Ficat and Arlet staging system in 1 femoral head, stage II in 44 femoral heads, stage III in 46 heads and stage IV in 20 femoral heads.



Graph 4: Bar chart showing Ficat & Arlet staging of AVN of the femoral head.

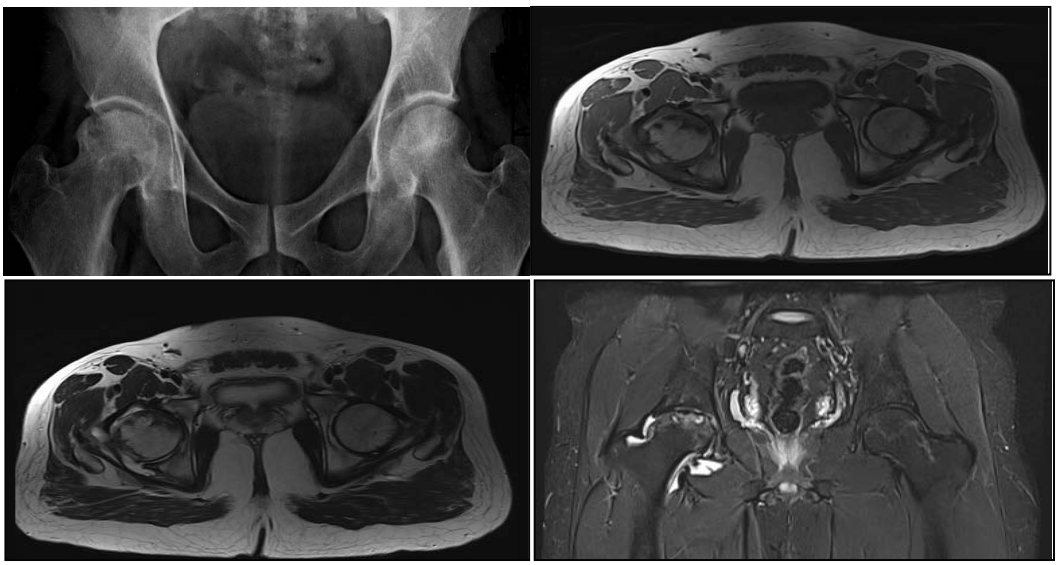
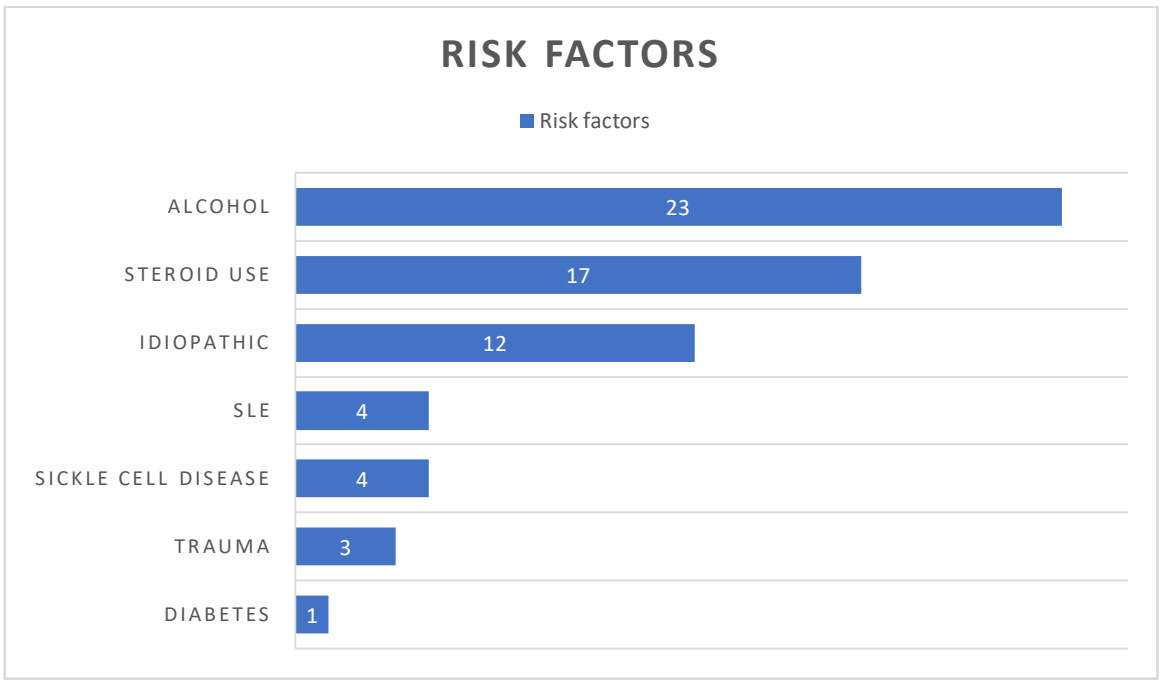


Fig. 1: AP radiograpgh pelvis (A) showing flattening and sclerosis of right femoral head and normal left head. Axial (B,C)T1,T2 and coronal STIR (C)) images with Geographic area of T1 hypointense, T2 heterogeneous hypointense, STIR heterogeneously hyperintensity involving head of the right femur with flattening, associated with mild right hip joint effusion. F/S/O right Grade – III AVN. T2 hyperintense area noted in ant sup aspect of left femoral head – S/o Edema – Grade – I AVN.

The analysis of risk factors in our study demonstrated that chronic alcoholism (35.5%) was the most common risk factor associated with AVN of femoral head followed by chronic steroid use (25.4%). other risk factors include Idiopathic(16.9%), sickle cell disease(6.7%), systemic lupus erythematosus(6.7%), trauma (5.08%), diabetes(1.69%).



Graph 5: Bar chart showing risk factors of avn.

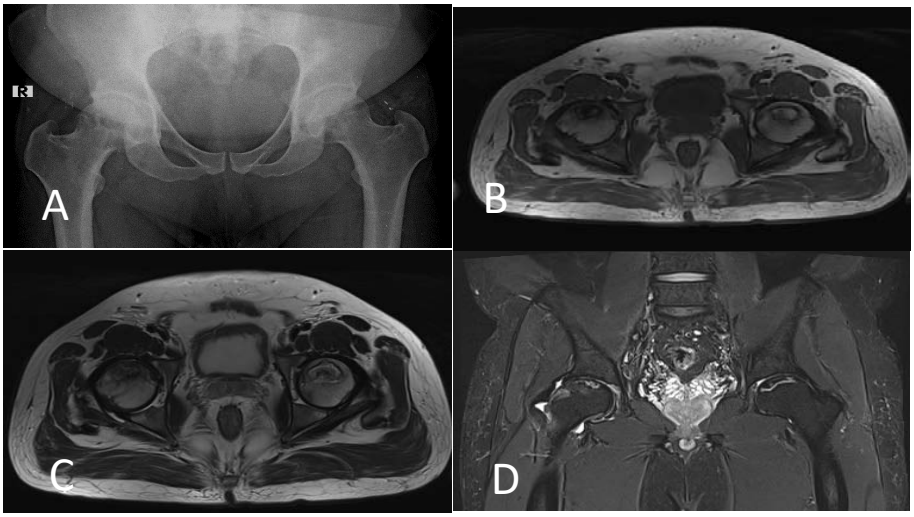


Fig. 2: AP radiograph pelvis(A) showing mild sclerosis of bilateral femoral heads with normal contour.MRI T1,T2 axial (B,C)and STIR coronal images(D) showing Geographical areas of altered signal intensity areas which are heterogeneously hyperintense on T1,T2 with surrounding hypointense rim with central suppression and peripheral hyperintense rim on STIR in both femoral heads. F/S/O bilateral grade II AVN.

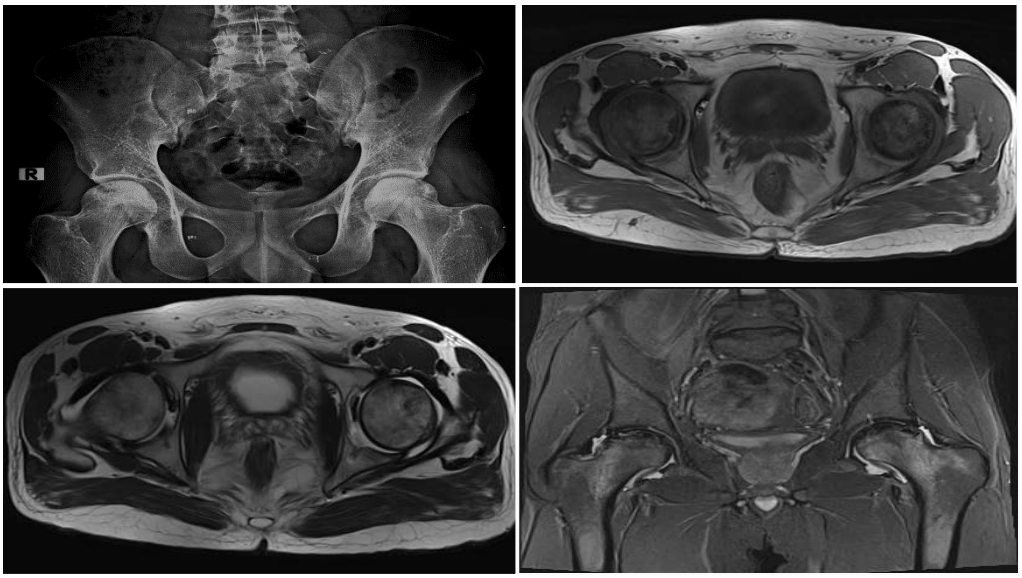
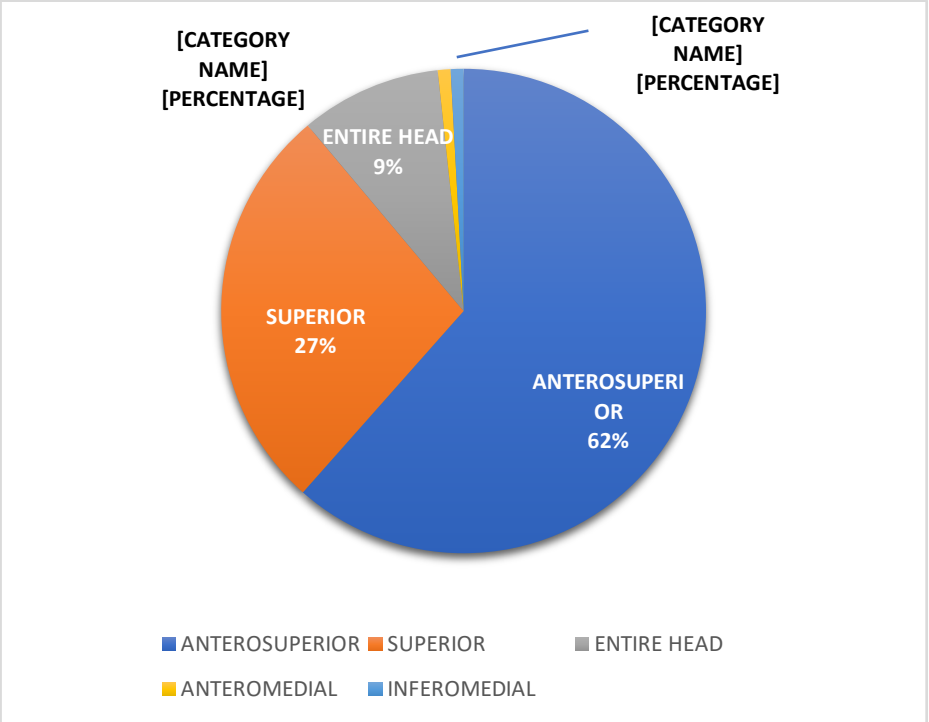


Fig. 3: AP radiograph pelvis(A) showing sclerosis of bilateral femoral heads with mild flattening.MRI t1,t2 axial (B,C) and coronal STIR images (D) showing Geographical altered signal intensity lesions in bilateral antero-superior aspect of femoral head, which appear heterogenous hyperintense on T1,T2 with surrounding hypointense rim, showing central suppression with peripheral hyperintense rim on stir in both heads with mild flattening and ass bilateral mild jointeffusion.
F/C/W Bilateral AVN of femoral heads – Stage III.

In this study, anterosuperior quadrant was involved in 72 (62%) of femoral heads followed by superior quadrant in 32 (27%), entire head was involved in 11(9%) heads, anteromedial and infero medial quadrants were involved in1 (1%) femoral heads each.



Graph 6: Pie chart showing quadrants involved AVN.

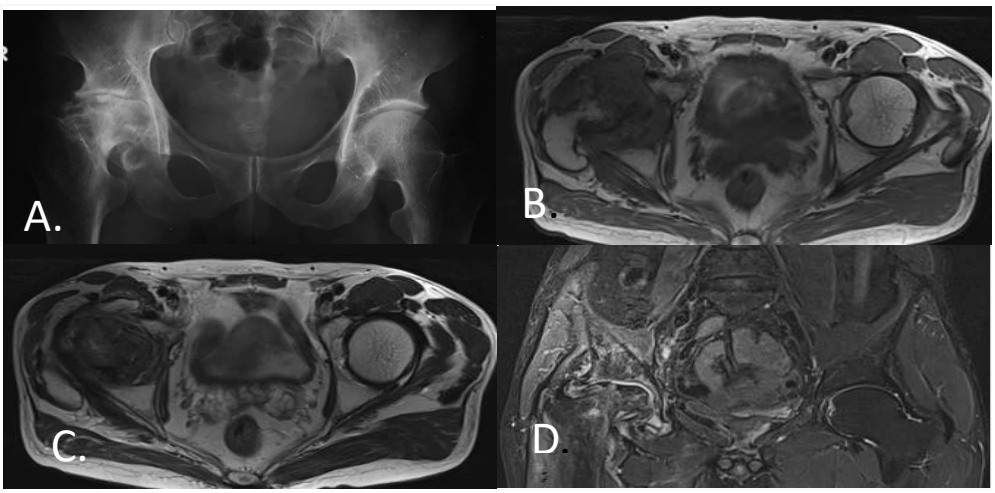


Fig. 4: This is Ap radiograph pelvis(A) showing reduced joint space and collapse of right femoral head with secondary osteoarthritic changes. (B,C) MRI T1,T2 axial and (D.) coronal STIR images showing altered signal intensity geographical area involving right femoral head which appears hypointense on T1,T2 and STIR with significant flattening and secondary osteoarthritic changes in femoral head and acetabulum associated with joint effusion and edema- F/S/O right stage IV AVN.

Analysis of MRI findings revealed that double line sign was most common finding seen in 85%femoral heads followed by loss of contour in 62%of heads, joint effusion was seen in 60% heads,bonemarrow edema in 50% and joint space reduction was noted in 18% of femoral heads.

Table 1: Analysis of MRI findings in AVN

MRI findings	No. of Femoral heads
Double line sign	99(84.6%)
Joint effusion	70(59.8%)
Bone marrow edema	59 (50.4%)
Subchondral collapse	33(28.2%)
Loss of joint space	21(17.9%)

Association of Joint effusion with staging showed that joint effusion was more common in stage 3and 4 that is 77% and 47.6% respectively followed by stage 2 in 46.5 %of femoral heads. A total of 70 out of 117 femoral heads showed joint effusion ie; 59.8%.

Table 2: Association of joint effusion with staging

Stage	Joint effusion	No of femoral heads	percentage
I	0	01	0%
II	20	43	46.5%
III	40	52	77%
IV	10	21	47.6
Total	70	117	59.8%

Association of marrow edema with staging showed that marrow edema was more common in stage 4 seen in 57.1% followed by stage 2 and 3 ie; 49 and 48 percent respectively.

Table 3: Association of marrow edema with staging

Stage	Bone marrow edema	No of femoral heads	percentage
I	1	1	100%
II	21	43	48.8%
III	25	52	48%
IV	12	21	57.1%
Total	59	117	50.4%

IV. Discussion

In this retrospective observational study of 64 patients, 45(70%) were males and 19(30%) were females with male to female ratio of 2.2:1. It shows higher prevalence of AVN in male than female population. This observation was similar to the study conducted by Jyothi choudary et al(1) in which 69% of the affected cases were males and 31% were females.

In our study AVN was found between age groups of 13 to 6o years with most of the patients 39(61%) belong to the age group of 21-40 years as the risk factors for AVN such as alcohol and steroids use most frequently occur in this age group. 16(25%) patients belong to the age group of 41 -50, 3(4.6%) patients belong to the age group of 51- 60 years and 6(9.3%)patients belongs to the age group of 11 -20.

The mean age of presentation was 34.2 years which is similar to the study conducted by Harsha vardhan et al(7) where the mean age was 34.7 years. There is statistically significant difference in the mean age of males and females with females being affected at a relatively younger age than males ($P<0.05$).

Bilateral disease 53 (83%) was more common than unilateral involvement 11(17%) in this study.

According to Ficat & Arlet classification of AVN, out of 117 femoral heads involved, we observed stage III was the commonest stage seen in 52 (44.4%) femoral heads followed by stage II in 43(36.7%) femoral heads. This was similar to study conducted by Jyothi choudary et al(1), in which stage III AVN was found in 39.4% femoral heads followed by stage II in 30.4% heads.

In this study, we found that alcohol was the most common associated risk factor for the avascular necrosis of femoral head seen in 23 patients (36%).

This finding is consistent with the study conducted by Mohammad Zeeshan Saleem et al(2) and Jacobs et al (6), in which alcohol was the most common associated risk factor in 56% and 39% respectively. The mean duration of intake of alcohol was 82 months in our study. In a study conducted by Harshavardhan et al(7), the mean duration of alcohol intake was 88months.

The exact mechanism of alcohol causing AVN is not known. However several studies have concluded that fat embolism linked to hyperlipidaemia which in turn leads to the blockage of blood supply to femoral head and eventually bone death.

The next common associated risk factor in our study is corticosteroid use in 17 patients (27%). Harsha Vardhan et al (7) in their study concluded that steroid was the most common risk factor associated with AVN.

The most common indication for steroid intake in out institute was SLE. Other indications include rheumatoid arthritis, glomerular nephritis, nephrotic syndrome, renal transplant, auto immune haemolytic anaemias, paraquet poisoning.

Though the pathogenesis of steroid induced AVN is not fully understood, the postulated mechanisms include fat hypertrophy, fat emboli and intravascular coagulation that leads to the impaired blood supply to bones.

Other risk factors in our study were sickle cell disease in 4(6%) patients, SLE in 4(6%) patients, trauma in 3(5%) patients, diabetes in 1(2%) patients and no identifiable cause was observed in 12 (19%) patients.

In this study 2 patients of sickle cell disease showed multiple bone infarcts involving iliac bones in addition to the AVN of femoral head.

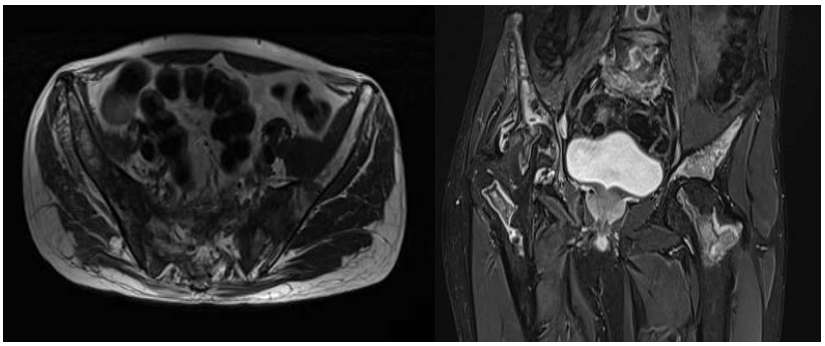


Fig. 5: Axial T2(A), and STIR coronal (B) images showing bilateral AVN with pelvic bone involvement.

The most common quadrant involved in our study is anterosuperior quadrant seen in 62% of the heads followed by superior quadrant in 27 % cases.

Gabriel et al(5), in their study showed that involvement of anterosuperior quadrant is specific for AVN. Nishii et al(3), in their study showed that location and size of the lesion are the prognostic indicators of collapse and large necrotic lesions have likelihood to involve anterosuperior quadrant.

In this study most common MRI finding of AVN is double line sign seen in 99 femoral heads (85%) which is considered pathognomic of AVN.

Other common findings are contour loss(62%), joint effusion (70%), bone marrow edema(50%), joint space reduction(18%).

In our study, joint effusion is seen in 70 out of 117 femoral heads(60%). The results of our study indicate that joint effusion is more prevalent in advanced stages of disease ie. stage III and stage IV. Out of 52 heads in stage III, 40 heads had joint effusion(76.9%) and out of 21 heads in stage IV, 10 heads had joint effusion(47.6%). 20 out of 43 heads of stage II heads had joint effusion(46.5%). Gou Chu Huang et al(8) and Mohammad Zeeshan Saleem et al(2), showed that stage III disease was most common to have joint effusion.

Bone marrow edema is seen in 50 out of 117 femoral heads(50.4%).

The results of our study showed that marrow edema is more prevalent in stage IV(51.1%) followed by stage II(48.8%) and stage III(48%).

In this study we have observed that 41 out of 59 osteonecrotic hips with marrow edema (81.3%) had associated joint effusion. The presence of joint effusion and bone marrow edema are prognostic factors for collapse. S Iida et al(4),In their study concluded that bone marrow edema was highly correlated with subsequent collapse.

V. Conclusion

As osteonecrosis of femoral head is increasingly becoming the cause of Musculoskeletal disability especially in younger age group, its early diagnosis is crucial because early interventions are associated with better prognosis.

This study shows that MRI is the imaging modality of choice. It helps in early diagnosis and better outcome and can also visualize the bone marrow changes, location and extent of area involved which are helpful when ascertaining patient prognosis and formulating plan of care.

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Acute Generalized Peritonitis due to Peritoneal Hydatid Cyst Rupture

By Outznit Mustapha, Lina Belkouchi, Laamrani F.Z & Jroundi Laila

Summary- Peritoneal hydatidosis is a rare and poorly known hydatid disease. Acute cyst rupture into the peritoneal cavity is one of its complications. We report a clinical case of a 25-year-old patient admitted to the emergency department for acute abdominal pain, the final diagnosis was acute peritonitis caused by the rupture of hydatid cyst into the peritoneal cavity associated with hepatic hydatidosis.

Keywords: *peritoneal hydatidosis, peritonitis, cyst, acute abdomen.*

GJMR-D Classification: *DDC Code: 616.362 LCC Code: RC846*

Strictly as per the compliance and regulations of:

Acute Generalized Peritonitis due to Peritoneal Hydatid Cyst Rupture

Péritonite Aigue Généralisée Par Rupture D'un Kyste Hydatique Péritonéal

Outznit Mustapha [α], Lina Belkouchi [σ], Laamrani F.Z [ρ] & Jroundi Laila [ω]

Résumé- **L'hydatidose péritonéale est une localisation rare et peu connue de la maladie hydatique. Parmi ses complications la rupture brutale d'un kyste hydatique dans la cavité péritonéale. Nous rapportons le cas d'un patient âgé de 25 ans admis aux urgences pour l'exploration d'un abdomen aigu dont le diagnostic final est une péritonite aigue généralisée par rupture d'un kyste hydatique intra-péritonéal associée à une hydatidose hépatique.**

Mots clés: hydatidose péritonéale, péritonite, kyste, abdomen aigu.

Summary- **Peritoneal hydatidosis is a rare and poorly known hydatid disease. Acute cyst rupture into the peritoneal cavity is one of its complications. We report a clinical case of a 25-year-old patient admitted to the emergency department for acute abdominal pain, the final diagnosis was acute peritonitis caused by the rupture of hydatid cyst into the peritoneal cavity associated with hepatic hydatidosis.**

Keywords: peritoneal hydatidosis, peritonitis, cyst, acute abdomen.

I. Introduction

La maladie hydatique est une anthropo-zoonose qui sévit à l'état endémique en région méditerranéenne, le péritoine au même titre que d'autres organes comme le foie peut être une localisation rare et grave de cette affection. L'objectif de cet article est de présenter, à travers un cas clinique d'abdomen aigu, les éléments sémiologiques d'une hydatidose péritonéale dans sa forme compliquée de rupture.

II. Observation Clinique

Il s'agit d'un jeune patient âgé de 25 ans, sans antécédents particuliers, qui consulte au service des urgences pour l'installation brutale d'une douleur abdominale généralisée après effort physique. L'examen clinique trouve un patient conscient, apyrétique et légèrement tachycarde. La palpation de l'abdomen objective une contracture généralisée avec une sensibilité plus marquée au niveau de la fosse iliaque gauche.

Une tomodensitométrie abdomino-pelvienne est réalisée sans et après injection de produit de contraste. Cette dernière, montre au niveau du foie droit de multiples formations kystiques, à contenu liquidien pur ou cloisonné, bien circonscrites, confluentes, à paroi épaissie rehaussées en périphérie après injection de produit de contraste en rapport avec des kystes hydatiques hépatiques de taille et de type variable.

Il s'y associe également au niveau pelvien deux kystes hydatiques intra-péritonéaux, le premier est multi vésiculaire et le deuxième sus et latéro-vésicale gauche à paroi affaissée, discontinue associée à un épanchement péritonéal témoignant sa rupture dans la cavité péritonéale.

Le diagnostic de péritonite aigue généralisée par rupture d'un kyste hydatique intra-péritonéal associée à une hydatidose hépatique est retenu.

III. Discussion

Le kyste hydatique est dû au développement de la forme larvaire du tænia du chien appelé *Echinococcusgranulosus*. C'est une zoonose cosmopolite, endémique dans les pays du Maghreb, l'Afrique de l'Est et l'Amérique du Sud .La contamination de l'homme se fait dans la majorité des cas après une ingestion d'aliments souillés par les fèces du chien infesté [1].

L'hydatidose péritonéale représente entre 5 et 16 % des hydatidoses [2]. Elle peut être primitive, par contamination hématogène. Elle est le plus souvent secondaire à une rupture kystique (kyste hydatique hépatique fréquemment associé) ou à une contamination per opératoire.

La symptomatologie clinique est variable et non spécifique, parfois de découverte fortuite du au développement lent du kyste hydatique après contamination.

Elle peut se manifester par une douleur abdominale chronique, nausées, vomissements et anorexie. Les formes compliquées des kystes demeurent dans la compression des organes de voisinage, une hémorragie intra-kystique, surinfection et rarement une rupture intra ou extra-péritonéale [3].

La rupture du kyste hydatique peut être spontanée par augmentation de la pression intra-kystique ou post-traumatique. Elle met en jeu le pronostic vital du fait de l'état de choc anaphylactique qu'elle peut engendrer. Elle se manifeste par une douleur abdominale sévère, des vomissements, une

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chute de la tension artérielle, une tachycardie voir des réactions allergiques [4].

Grace à l'imagerie médicale, le diagnostic de cette entité devient de plus en plus facile et rapide. L'échographie abdominale et la tomodensitométrie ont respectivement une sensibilité de 85% et 100% [5].

L'échographie abdominale est réalisée en première intention permettant ainsi de confirmer le diagnostic en précisant la localisation du kyste, le nombre et ses rapports anatomiques .Toute fois sa résolution spatiale est limitée comparativement à la tomodensitométrie qui permet une analyse plus précise de l'environnement du kyste [6].

Le traitement médical initial est basé sur les mesures de réanimation en cas de choc anaphylactique par l'administration des drogues vasoactives, remplissage et monitorage. Ensuite une toilette péritonéale abondante est réalisée par le sérum physiologique avec aspiration. La technique chirurgicale de choix dans le contexte d'urgence est la résection du dôme saillant qui est une méthode facile et adaptée aux pays d'endémie [7].

IV. Conclusion

La rupture aigue d'un kyste hydatique dans la cavité péritonéale est un phénomène rare mettant en jeu le pronostic vital. Elle doit être toujours suspectée dans les pays d'hyper endémie hydatique. L'échographie et la tomodensitométrie permettent un diagnostic précoce de cette complication.

Déclarations des auteurs

Les auteurs déclarent ne pas avoir de conflit d'intérêt en relation avec cet article.

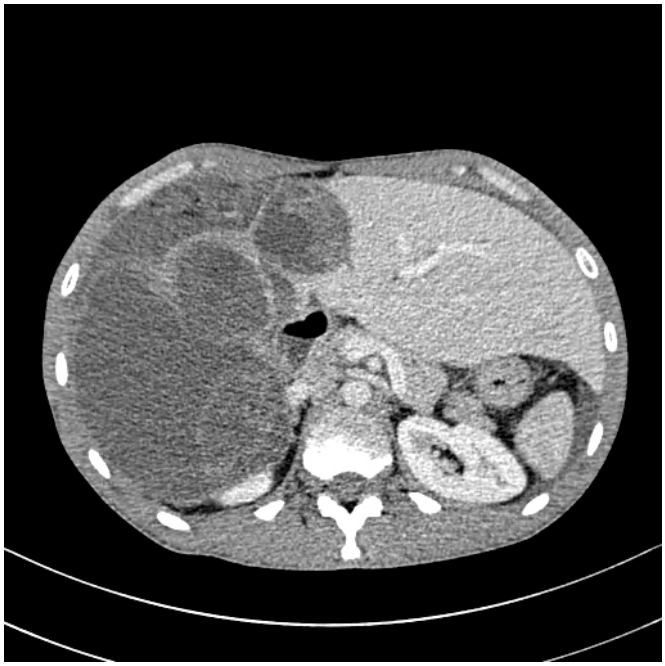

Figure 1A

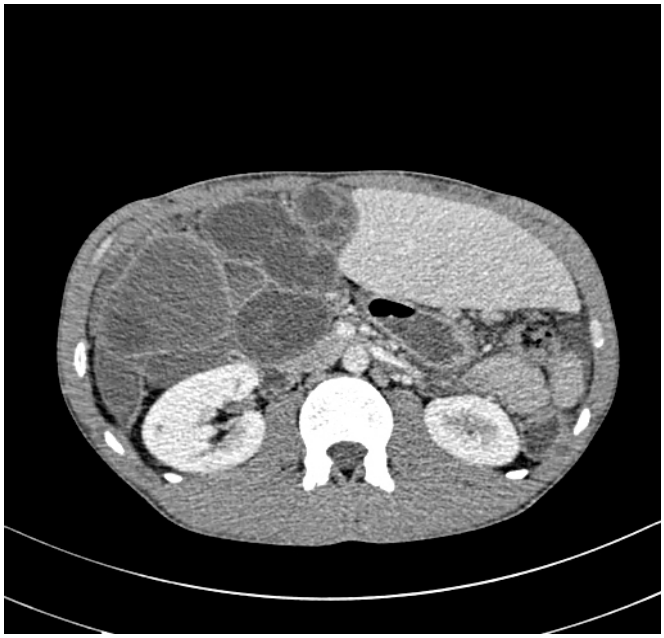

Figure 1B

Figure 1A et 1B: TDM abdominale en coupe axiale montrant la présence de multiples kystes hydatiques du foie droit.

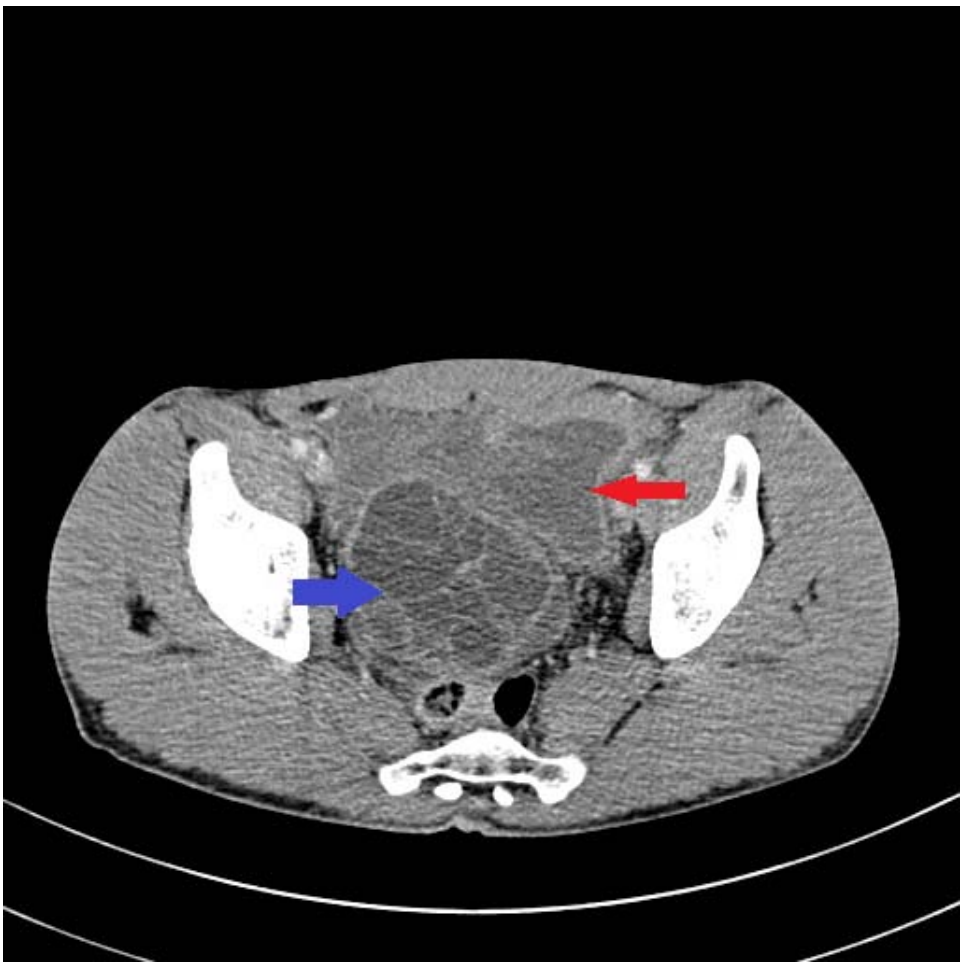

Figure 2A

Figure 2A: TDM pelvienne en coupe axiale montrant la présence d'un kyste hydatique multi vésiculaire (flèche bleue) et un autre sus et latéro-vésical gauche à paroi affaissée et discontinue (flèche rouge) associée à un épanchement péritonéal témoignant de sa rupture aigue.

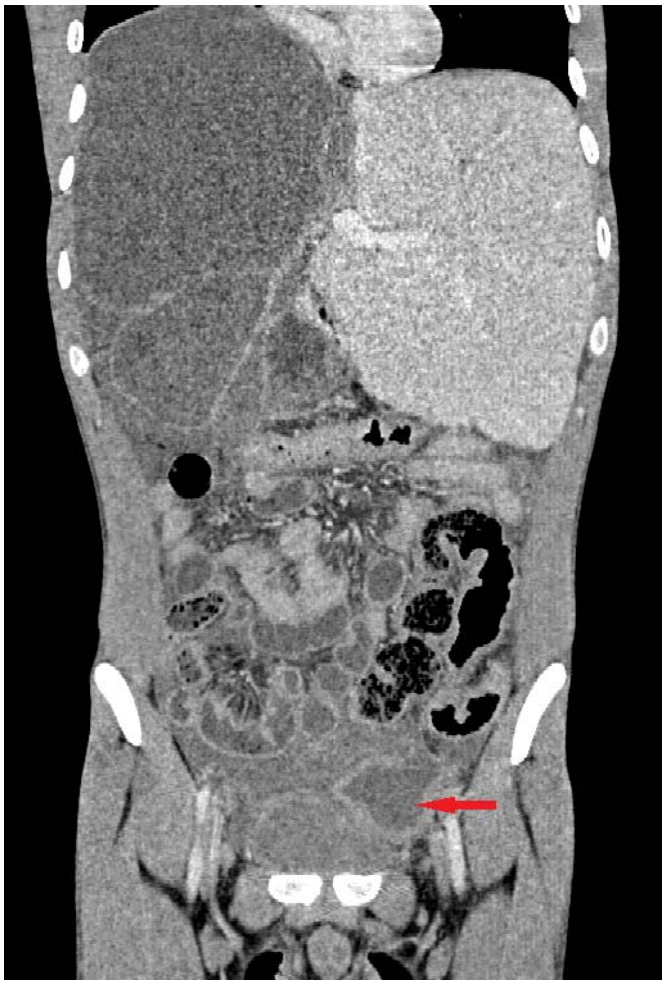

Figure 2B

Figure 2B: Reconstruction coronale.

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The Comparison Study of Lung Computerized Tomography Severity Score and Vaccination Status in Covid-19 Patient's

By Dr. Rohith Sandesari, Dr. T Rajani & Dr. Jyostna Rani Y

Abstract- In the COVID-19 pandemic, HRCT chest is often used by clinician to determine extent of their lung involvement. The aim of this study is to assess the severity of lung involvement in confirmed/suspected COVID-19 patients and its correlation to vaccination status, with either COVISHIELD or COVAXIN, in a tertiary care center. This is a retrospective study, in which our data is analyzed from 1st April 2021 to 30th April 2021, to identify patients (>16 years) who had confirmed (positive RT-PCR or antigen test) and received a HRCT Chest within 1st week (Avg <3.5 days) of RT-PCR Positive test, to determine the extent of their lung involvement using the CT severity score (CT-SS). Patients were classified in 3 groups based on their vaccination status to determine its correlation with the CT-SS score: fully vaccinated (received 2 doses of vaccine), partially vaccinated (one dose of vaccine), and unvaccinated. Basic descriptive statistics, Student t test and ANOVA test were done using Epi-info 7.1 software M.S.Windows.

Keywords: *COVID-19-Coronavirus 2019 or SARS-CoV2 infection; HRCT-high resolution computerized tomography; CT-SS-computerized tomography severity score; RT-PCR-reverse transcription polymerase chain reaction.*

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The Comparison Study of Lung Computerized Tomography Severity Score and Vaccination Status in Covid-19 Patient's

Dr. Rohith Sandesari [α], Dr. T Rajani [σ] & Dr. Jyostna Rani Y [ρ]

Abstract- In the COVID-19 pandemic, HRCT chest is often used by clinician to determine extent of their lung involvement. The aim of this study is to assess the severity of lung involvement in confirmed/suspected COVID-19 patients and its correlation to vaccination status, with either COVISHIELD or COVAXIN, in a tertiary care center. This is a retrospective study, in which our data is analyzed from 1st April 2021 to 30th April 2021, to identify patients (>16 years) who had confirmed (positive RT-PCR or antigen test) and received a HRCT Chest within 1st week (Avg <3.5 days) of RT-PCR Positive test, to determine the extent of their lung involvement using the CT severity score (CT-SS). Patients were classified in 3 groups based on their vaccination status to determine its correlation with the CT-SS score: fully vaccinated (received 2 doses of vaccine), partially vaccinated (one dose of vaccine), and unvaccinated. Basic descriptive statistics, Student t test and ANOVA test were done using Epi-info 7.1 software M.S.Windows. A total of n=175 patients (median age 51 years, 66.3% male; 33.7% female) of which 158 (90%) had confirmed COVID-19 positive RT-PCR and 17(10%) had disease with classic symptoms and rapid antigen test positive for COVID 19. Of the 175 patients 34 (19.4%) had complete vaccination, 63 (36%) had partial vaccination and 78(44.6%) had no vaccination. The CT severity score of the completely vaccinated patients was significantly lower (i.e., between 0 to 2), compared to partially vaccinated (i.e., between 2 to 18) & unvaccinated patients (i.e., between 2 to 23). The mean CT-SS of vaccinated, partially vaccinated & unvaccinated is 0.23 ± 0.11, 6.98 ± 0.62, &11.46 ± 0.73, respectively p<0.001. A multivariate linear regression model showed that partial or fully vaccinated patient's had lower CT severity score compared to vaccinated patients (adjusted R squared = 0.41). CT severity score in fully vaccinated patients is significantly lower compared to partially vaccinated or unvaccinated patients. Complete vaccination in patients could be critical in preventing severe lung disease. However, we found no significant difference in CT-SS of vaccinated patients who had taken either COVISHIELD or COVAXIN.

Keywords: COVID-19-Coronavirus 2019 or SARS-CoV2 infection; HRCT-high resolution computerized tomography; CT-SS-computerized tomography severity score; RT-PCR-reverse transcription polymerase chain reaction.

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I. Introduction

Coronaviruses are a family of viruses that usually causes illness such as the common cold, severe acute respiratory syndrome (SARS).In March of 2019, a new coronavirus was identified as the cause of a pneumonia outbreak that originated in China. This Causative virus was initially termed as "Novel corona virus 2019" ,by WHO, later a coronavirus study group (CSG) Renamed the virus as "Severe acute respiratory syndrome corona virus 2" aka "SARS-CoV-2" and the it causes is called as "Corona virus disease 2019" aka "COVID-19". In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. The virus spreads by direct means such as droplet spread or by indirect means such as airborne spread. Due to longer incubation periods and contagiousness of the disease, the disease spreads rapidly in population cluster. Some patients can also be asymptomatic accelerating the spread of disease.

Elder population are usually at high risk of serious illness from COVID-19.The risk increases with age. There are certain medical conditions that increase risk of serious illness from Covid19, such as Heart disease, Cancer, Chronic obstructive pulmonary disease, Diabetes, Obesity, Hypertension, smoking, chronic kidney disease, weakened immune system, asthma, liver disease. On HRCT, Ground glass opacities are the areas of the increased lung opacity where underlying broncho vascular markings are not obscured. Ground glass opacity is usually the most common manifestation of Covid-19 pneumonia on HRCT chest imaging. Both lower lobes are the usually the most commonly involved. Often the common finding is multiple focal ground glass opacities in both lung fields. Reversed halo sign is also a typical finding visualized on HRCT. However there a few indeterminate findings noted are Diffuse ground glass opacities without any clear distribution, Nodular opacities with ground glass halo, focal consolidations and centrilobular nodules.

However, COVID-19 pneumonia sometimes, may manifest as unilateral Ground glass opacity, before the onset of symptoms with rapid progression into diffuse disease involving both lung fields. On 1 January 2021, the Drug Controller general of India (DCGI) approved emergency use of the Oxford-AstraZeneca

vaccine (local trade name "Covishield"). On 2 January, the DCGI also granted an interim emergency use authorization BBV152 (trade name "Covaxin"), a domestic vaccine developed by Bharat Biotech in association with the Indian Council of Medical research and National Institute of Virology. Both of them require 2 doses for complete vaccination with a interval 30 days in between both the doses.

The main objective of the study is to assess the severity of lung involvement in RT-PCR confirmed COVID-19 patients. And also to assess the severity of lung involvement to vaccination status, with either COVISHIELD or COVAXIN, and also with co-morbidities.

II. Materials and Methods

This is a retrospective study done in the Department of Radiology and Imageology in a tertiary care center. The data is analyzed from 1st April 2021 to 30th April 2021, to identify patients (>16 years) who had confirmed (positive RT-PCR + SYMPTOMS) and underwent a HRCT Chest within 1st week (Avg <3.5 days) of RT-PCR Positive test (False positive rate 0.8-1.3%), to determine the extent of their lung involvement using the CT severity score (CT-SS).

All the patients (n=175) have undergone a standardized HRCT chest imaging protocol with single inspiratory breath hold. CT Images of the chest were obtained on a 16slice multidetector CT Unit (Philips Brilliance MRC 600) with 8—120 kVp, 20-40 mAs tube current, slice section of 1.5 mm, rotation 0.5, Matrix 512 x 512. Patients were classified in 3 groups based on their vaccination status to determine its correlation with the CT-SS score: fully vaccinated (received 2 doses of vaccine), partially vaccinated (one dose of vaccine), and unvaccinated.

All the cases were reviewed by two independent radiologist with 15 years and 2 years of experience and were blinded to the history. In all cases, semiquantitative CT severity scoring was calculated per each of the 5 lobes considering the extent of anatomic involvement, as follows: 0-No involvement; 1-< 5% involvement; 2- 5–25% involvement; 3- 26–50% involvement; 4- 51–75% involvement; and 5- > 75% involvement. The resulting CTSI score was the sum of each individual lobar score and (0 to 25). The CTSI scoring was classified into 3 groups (1)mild involvement with CTSI score 1-9 ;(2) moderate involvement with CTSI score 10-17;(3) severe involvement with CTSI score 18-25.

III. Statistical Analysis

Basic descriptive statistics were reported as frequencies and means. Student t test and ANOVA test were done and p value <0.05 was defined as statistically significant. The analysis was performed using Epi-info 7.1 software M.S.Windows.

IV. Results & Observations

A total of n=175 patients were included in the study who have been confirmed cases of COVID -19 pneumonia by RT-PCR test and having symptoms. Almost 116 patients i.e 66.3% of the study population was Males& n=59 patients (33.7%) were females. Majority of the study population i.e, 45.7% was observed in the age group of 45-59 years when compared to other age groups. The Mean age of the study population was 49.03 years ± 1.11.

Approximately 20% (n=34) of the study participants had taken 2 doses of COVID Vaccine (COVAXIN/COVISHIELD). Approximately 44.6% (n=78) of the study participants were not vaccinated.

The mean CTSI is higher in patients with co-morbidities compared to patients with no underlying condition. The mean CTSI in patients with Co-morbidities is 13.1 ± 4, whereas in patients with no co-morbidities is 6 ± 3.2.

The mean CTSI value of the study participants was 7.57 ± 0.5.Majority (i.e 30 out of 35) of the study participants with no lung involvement were fully vaccinated which was statistically significant (p<0.001). Majority of the study participants (i.e 30/34) who were completely vaccinated had no involvement of lung and only few had mild involvement of the lung. This observation is statistically highly significant (p<0.001).

The CT severity score of the completely vaccinated patients was significantly lower (i.e., between 0 to 2), compared to partially vaccinated (i.e., between 2 to 18) & unvaccinated patients (i.e., between 2 to 23). The mean CT-SS of vaccinated, partially vaccinated & unvaccinated is 0.23 ± 0.11, 6.98 ± 0.62, & 11.46 ± 0.73, respectively p <0.001.

V. Discussion

Approximately 20% (n=34) of the study participants had taken 2 doses of Covid Vaccine, which is higher than the India National average of 9.7% according to WHO. Approximately 44.6% (n=78)of the study participants was not vaccinated, which is less than the National average of 80.3% (according to WHO).The higher average vaccination status can be attributed to the fact that this is tertiary care center in a metro city where most of the population has access to the vaccine. The mean CTSI is higher in patients with co-morbidities compared to patients with ncondition. The mean CTSI in patients with Co-morbidities is 13.1 ± 4, whereas in patients with no co-morbidities is 6 ± 3.2. This observation is statistically significant (p-value<0.05) and is consistent with previous studies.

The mean CTSI value of the study participants was 7.57 ± 0.5. Most of the study population were having mild Lung Involvement based on CTSI. According to the study conducted by Marco et al, the

average CTSI in the population is 6.1 ± 1 with mild lung involvement, which is comparable to our study.

Majority (i.e 30 out of 35) of the study participants with no lung involvement were fully vaccinated which was statistically significant ($p<0.001$) Majority of the study participants (i.e 30/34) who were completely vaccinated had no involvement of lung and only few had mild involvement of the lung. This observation is statistically highly significant ($p<0.001$). Among the vaccinated patients, there was no significant difference in CTSI between COVISHIELD (mean CTSI 0.22 ± 0.8) and COVAXIN (mean CTSI 0.23 ± 0.3).

The CT severity score of the completely vaccinated patients was significantly lower (i.e., between 0 to 2), compared to partially vaccinated (i.e., between 2 to 18) & unvaccinated patients (i.e., between 2 to 23). The mean CT-SS of vaccinated, partially vaccinated & unvaccinated is 0.23 ± 0.11, 6.98 ± 0.62, & 11.46 ± 0.73, respectively $p<0.001$. This is comparable to the other similar studies done by Jaimin et al., University of Louisville School of Medicine. A multivariate linear regression model showed that partial or fully vaccinated patient's had lower CT severity score compared to vaccinated patients (adjusted R squared = 0.41).

Our study has few limitations. The study is done in a single tertiary care center, thus could have a selection bias affecting the generalizability of the study. Only 20% (40/175) of our study population is completely vaccinated. A study population with higher vaccination status compared to unvaccinated could give a better comparison and analysis

VI. Conclusion

CT severity score is higher in patients with Co-morbidities compared to patients with no underlying medical condition. CT severity score in fully vaccinated patients is significantly lower compared to partially vaccinated or unvaccinated patients. Complete vaccination could be critical in preventing severe lung disease. However, we found no significant difference in CT-SS of vaccinated patients who had taken either COVISHIELD or COVAXIN.

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Associates are authorized to organize symposium/seminar/conference on behalf of Global Journal Incorporation (USA). They can also participate in the same organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent. Additionally, they get free research conferences (and others) alerts.

Career | Credibility | Financial

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Preferred Author Guidelines

We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

Alternatively, you can download our basic template from https://globaljournals.org/Template

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Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

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It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

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Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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