TALLINN UNIVERSITY OF TECHNOLOGY
School of Information Technologies
Department of Health Technologies

Jevgenia Hammerberg 153685YVEM

EVIDENCE ON THE POSSIBLE APPLICATION OF ULTRASOUND TECHNOLOGY IN AESTHETIC MEDICINE FOR HYALURONIC ACID FILLERS USAGE- A STATE-OF-THE-ART REVIEW

Master's thesis

Supervisor: Riina Hallik
Msc, MMS, RN.

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Infotehnoloogia teaduskond

Jevgenia Hammerberg 153685YVEM

TÕENDID ULTRAHELI TEHNOLOOGIA RAKENDAMISE VÕIMALUSTE KOHTA ESTEETILISES MEDITSIINIS HÜALUROONHAPPE TÄITEAINETE KASUTAMISE VAATEKOHAST - KAASAEGSE KIRJANDUSE ÜLEVAADE

Magistritöö

Juhendaja: Riina Hallik
Msc, MMS, RN.

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

Author: Jevgenia Hammerberg

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Abstract

Introduction The research problem at hand is that ultrasound (US) implementation into practice is highly promoted and popularized in aesthetic medicine field, however, the evidence concerning US useability and effectiveness is still lacking, as effects and applications of US for aesthetic medicine are not researched well. Thus, a literature review is needed to explore the evidence in order to understand if it would provide grounds for the introduction of ultrasound into routine aesthetic practice. *The aim* of this study is to explore the current state of US technology usage in aesthetic medicine in terms of HA injectables. *Method* A state-of-the-art review was carried out. The search was conducted in three medical electronic databases: Embase, Science direct and PubMed. Four out of five steps of systematic reviews were followed - no formal quality assessment was applied for obtained articles. *Results* 47 articles published between 2008 and 2021 were included in the study which shows that active use of ultrasound in aesthetic medicine has been developed only in recent years. Overall majority of included papers provide broad analytical and informative reflections on the concepts of US applications for aesthetics. Pre-procedural US allows to visualise blood vessels, post-procedural US may help to detect adverse reactions. The effectiveness of US depends on the operator, who needs skill and constant practice to become well versed in its use. Concerning evaluation of filler sonography without reference to operator's frailty, findings show that in more than 97,5% and up to 100% cases provided by radiologists it was possible to assess and identify fillers with sonography, this finding further support the affirmations of some authors that sonography is the first-choice imaging modality for detection, identification, and complication management of injectable fillers. *Conclusion* The current state of literature regarding application of US for aesthetics does not provide evidence-based recommendations and guidelines. US usage was found to have no support data or provement that US application improves safety and eliminates complications in aesthetics. To provide correct US examination and obtain reliable results - essential knowledge of accurate use of the device and the ability to interpret sonographic findings are crucial. Further research based on methodology including proper quality assessment would provide reliable scientific evidence on US usage, strong enough for evidence-based authority for further implication of US into aesthetics. This thesis is written in English and is 75 pages long, including 6 chapters, 8 figures and 1 table.

Annotatsioon

Tõendid ultraheli tehnoloogia rakendamise võimaluste kohta esteetilises meditsiinishüaluroonhape täiteainete kasutamise vaatekohast- Kaasaegse kirjanduse ülevaade

Sissejuhatus Uurimisprobleemiks on see, et ultraheli rakendamist praktikasse propageeritakse ja populariseeritakse esteetilise meditsiini valdkonnas, kuid tõendid ultraheli kasutatavuse ja tõhususe kohta on endiselt puudulikud, kuna ultraheli mõju ja rakendusi esteetilises meditsiinis ei ole uuritud hästi. Seega on tõendite uurimiseks vaja kirjanduse ülevaadet, et mõista, kas see annaks aluse ultraheli kasutuselevõtuks rutiinsesse esteetilisesse praktikasse. Selle uuringu *eesmärk* on uurida ultraheli tehnoloogiakasutuse hetkeseisu esteetilises meditsiinis hüaluroonhape täitesüstide osas. *Meetod* Viidi läbi kaasaegne ülevaade. Otsing viidi läbi kolmes meditsiinilises elektroonilises andmebaasis: Embase, Science direct ja PubMed. Järgiti nelja süstemaatilise ülevaate etappi viiest – saadud artiklitele ei rakendatud formaalset kvaliteedihinnangut. *Tulemused* Uuringusse kaasati 47 aastatel 2008-2021 avaldatud artiklit, mis näitavad, et ultraheli aktiivne kasutamine esteetilises meditsiinis on arenenud alles viimastel aastatel. Üldiselt pakub enamik kaasatud dokumente laialdasi analüütilisi ja informatiivseid mõtteid ultraheli kontseptsioonide kohta. Protseduurieelne ultraheli kasutamine võimaldab veresooni visualiseerida, protseduurijärgne ultraheli kasutamine võib aidata tuvastada kõrvaltoimeid. Ultraheli tõhusus sõltub operaatorist, kes vajab selle kasutamisega hästi kursis olemiseks oskusi ja pidevat harjutamist. Mis puudutab täidissonograafia hindamist ilma operaatori nõrkusele viitamata, siis leiud näitavad, et enam kui 97,5% ja kuni 100% radioloogide esitatud juhtudest oli võimalik täidiseid hinnata ja tuvastada sonograafia abil, see leid toetab veelgi mõnede autorite kinnitusi, et sonograafia on esmavaliku visualiseerimismeetod süstitavate täiteainete tuvastamiseks ja tüsistuste korrigeerimiseks. *Järeldus* Kirjanduse praegune seis ultraheli esteetika kasutamise kohta ei anna tõenduspõhiseid soovitusi ja juhiseid. Leiti, et ultraheli kasutusel puuduvad tugiandmed või tõendid selle kohta, et selle rakendus parandab ohutust ja välistab hüaluroonhape täitesüstidega seotud tüsistused. Õige ultraheli uuringu läbiviimiseks ja usaldusväärsete tulemuste saamiseks on olulised teadmised seadme täpse kasutamise kohta ja sonograafiliste leidude tõlgendamise oskus. Täiendav uurimus, mis põhineb metodoloogial, mis hõlmab mh kohast kvaliteedi hindamist, annaks usaldusväärsed teaduslikud tõendid ultraheli kasutamise kohta ning oleks piisav

tõenduspõhine alllikas ultraheli edasiseks kasutamiseks esteetika valdkonnas. See lõputöö on kirjutatud inglise keeles ja on 75 lehekülge pikk, sisaldab 6 peatükki, 8 joonist ja 1 tabelit.

List of abbreviations and terms

US	Ultrasound
HA	Hyaluronic acid

Table of contents

List of figures

List of tables

1 Introduction

Current work lies within aesthetic medicine field but only within the method of injectable fillers. Injectables deliver quick results to the patient, providing anti-aging effect on wrinkles and sagging skin. The most popular is temporary filler containing hyaluronic acid (HA), which is also the focus of this thesis. The significant reason for preferring HA products by patients or practitioners is it's biodegrability, safe and natural results, and potential reversibility in case of undesirable outcome [1] This method has developed rapidly in recent years [2], [3]. There were more than 3,4 million injectable procedures performed only in the United States of America in 2020 and the usage of injectables compared to 2016, was increased by 24,1% [4]. From years 2000 to 2017, the growth was 250% [5]. In Estonia the discipline has been growing rapidly since 2005, when first day spas and aesthetic medicine clinics were founded, nevertheless, there is no data collected in Estonia concerning HA fillers usage.

Despite the large number of recommendations and instructions for the prevention and treatment of undesirable consequences such as knowing the anatomy, avoidance of dangerous zones, cannula usage for injection and aspiration [6], [7], [8], it is impossible to prevent all possible complications [9]. Anatomy knowledge may minimize the incidence of vascular complications; however, the distribution of blood vessels may vary depending on patient [8] and aspiration practice might appear ineffective [10], [11]. Taking this into account, there is a need for imaging technique to visualize subdermal anatomy to examine tissues before and after treatment [12]. Latest developments in healthcare technologies allow to assess the soft tissues and blood vessels of the face before and after the procedure, to ensure the safety of the treatment or urgent assessment of complications [12] [13]. Ultrasound (US) examination seems like a unique tool and quality standard that might be used for aesthetic medicine to examine or prevent the side-effects of wrinkle fillers [14]. Since this technology is not common in aesthetic medicine, the possible usage may present many questions for specialists, especially those, who are not experts in sonography, might need to use US in everyday practice while injecting fillers [15], [16], [17]. This situation of uncertainty is relevant worldwide as several machines are presented and promoted on the market for aesthetic usage, their useability is widely propagated on professional conferences (IMCAS, AMWC), several guidelines and imaging description

specifications were proposed by US usage pioneers [15], [16], [17], [18], [19]. However, research concerning US useability and evidence-based effectiveness is needed [20], [21], [22]. Young et al [22] in 2008 and Schelke et al [21] in 2010 wonder also whether US may add value for complication treatment and injectable filler assessment and recommend further investigation and evaluation on a basis of a larger clinical data.

Further research concerning US technology effect on HA injectables administration management shall provide more evidence concerning technology implementation outcomes, and potentially as a possible and desirable result - safety improvement. Thus, a state-of-the-art review is needed to see whether research on US usage for injectable filler outcome assessment has been carried out and provided statistically relevant results so that it would provide grounds for the introduction of US into routine aesthetic practice.

The research problem at hand is that US implementation into practice is highly promoted and popularized in aesthetic medicine field, however, the evidence concerning US useability and effectiveness is still lacking, as effects and applications of US for aesthetic medicine are not researched well.

The aim of this study is to explore the current state of US technology usage in aesthetic medicine in terms of HA injectables.

The objectives are:

1. To show the evolvement of US usage in aesthetic medicine field.
2. To outline main types of US applied for aesthetic medicine usage.
3. To present possible applications and indications for US imaging in aesthetic medicine.
4. To evaluate the usefulness of US technology in terms of improving the usage of HA injectables.
5. To outline main requirements for conducting correct US examination in aesthetics.

The research questions are:

1. How has the US usage in aesthetic medicine field evolved?
2. What are the main types of US used in aesthetic medicine?
3. What are the main possible applications and indications for US imaging/examination in aesthetic medicine?

4. How useful is US technology in terms of improving the usage of HA injectables?
5. What are the main requirements for conducting US examination in aesthetics properly?

Aim was achieved by presenting the current overview about the possibilities for application and the usefulness of US implementation into aesthetic practice. All research questions have been answered and point out that pre-procedural US allows to visualise blood vessels and post-procedural US may help to detect adverse reactions, though for reliable outcome operators' expertise is very important. The central argument of the thesis is that in the field of aesthetic medicine US is a useful tool for facial structures and anatomy evaluation in terms of pre- and postprocedural assessment for HA filler treatment evaluation, however the current state of literature does not provide evidence-based recommendations and guidelines. The study highlights factors that need to be considered for providing proper and legitimate US examination.

The author has had 15 years of practice in aesthetic medicine with injectables. Main reason for choosing this topic is a great aspiration to contribute to aesthetic procedures safety in Estonia, spread the knowledge and promote safe practice, as it appears of importance in terms of rapidly developing "beauty business".

As the usage of US technology is not yet implemented into Estonian aesthetic medicine practice the current thesis is needed in order to give an overview of HA fillers management with US. It is relevant for medical professionals who need information for potential US implementation into everyday practice and to gain an understanding of safe aesthetic practice for prevention, diagnosis and treatment of complications.

Given thesis consists of six chapters. The first chapter is an introduction to the field and the problem of research. The second chapter reflect the actual situation in the field, main issues with injectables in aesthetics and US technology considerations. The third chapter covers the research process and methodology aspects, the results of the research are presented in fourth chapter. The fifth chapter discusses the state-of-the-art study results and covers limitations of the study and future recommendations for research. In the sixth chapter conclusion of the study is presented.

2 Background

The current thesis lies withing the fields of aesthetic medicine and US. The next chapters will give and overview of the terminology and field development along with advantages for HA filler usage technological considerations for US usage.

2.1 Aesthetic medicine and injectable fillers

Aesthetic medicine is defined by **International Association for Physicians in Aesthetic Medicine (2022) as** "A branch of medicine focused on satisfying the aesthetic desires and goals of patients. This specialty is primarily focused on the pathophysiology of aging skin and adheres to scientific based procedures. Physicians practicing aesthetic medicine are trained in both invasive and non-invasive treatment modalities, and typically utilize a combination to meet the needs of the patient" [23]**.** Aesthetic medicine generally focuses on altering the cosmetic appearance with treatment improving skin conditions such as wrinkles, laxity, moles, pigmentation, body conditions such as cellulite, excess fat, unwanted hair growth, visible spider veins [24]. Methods included are from dermatology, reconstructive or plastic surgery fields with minimally invasive non-surgical procedures with injectables or lasers, methods may be combined for better outcomes [23].

In the beginning of aesthetic medicine development in France 40 years ago, at first, procedures to improve the appearance were only surgical, and at that time, specialists had very few methods and procedures that they could offer their patients to treat aesthetic problems of the face and body [24]. Aesthetic medicine in its current conception has developed thanks to discoveries and innovations in various fields of medical and surgical specialties: ophthalmology, dermatology, gynaecology, plastic and general surgery, and therefore nowadays seen as an eclectic collection of techniques or practices derived or evolved from different disciplines [25].

Aesthetic medicine and plastic surgery are supplemented annually with new methods for correcting age-related changes. A wide range of technologies allows specialists to solve patient appearance issues not only by surgery, but also with minimally invasive procedures [4], [5]. One of the methods of treatment of senile atrophy of the skin (ICD-10 code, L 57.4 Cutis laxa senilis) and non-surgical facial enhancement is soft tissue augmentation with fillers, which is carried out at several levels: dermal, hypodermal and supraperiosteal. When drawing up a plan

for the correction of a particular area of the face, health professionals choose the type of filler, its density, and plan the volume of the product to be injected for the desired outcome.

Although various fillers have been used in aesthetic medicine for a long time, the development and adoption of new generations of HA fillers has revolutionized the practice of soft tissue augmentation, providing safe and effective tool for wrinkle filling [25]. There are several different types of dermal fillers on the market: temporary fillers such as HA, calcium hydroxyapatite, poly-L-lactic acid, polycaprolactone; permanent fillers include mainly PMMA, polyacrylamide, polyalkylimides, and liquid injectable silicone [26]. HA fillers might be dissolved with hyaluronidase if complications or undesirable outcome arise [1].

In recent years, the desire of patients to look and feel younger has stimulated the field of aesthetic medicine to evolve and offer more new procedures and techniques. To date, aesthetic medicine has many tools to offer the patient solutions and treatment for most disorders and complaints to improve appearance. The most popular methods and non-surgical procedures among patients are botulinum toxin injections to correct mimic wrinkles, injections of various fillers to correct tissue volume loss, laser and other skin resurfacing treatments, removal of wrinkles, scars and pigmentation [24], [25], [27], [28].

Life expectancy is increasing, and aesthetic medicine is on the rise. The developments in aesthetic medicine injectables offer patients a better well-being through aesthetic treatments, correcting the signs of skin aging and treatments to prevent aging. However, it is important that all practitioners share the importance of a safe approach to procedures so that her future is bright. Safety is the most important issue in the discipline of aesthetic medicine and aesthetic medicine professionals know that science is fundamental to safety [24].

Recently, with the development of various techniques, the highest attention is also paid to the anatomy of the patient and the safety aspects of the procedures [6], [7], [29]. One of the latest recommendations for improving safety of aesthetics and management of injectable complications is US usage implementation into practice [2], [3], [13], [22], [14]. US usage is very widespread throughout every field of medicine. Many medical specialties have adopted the use of US as a painless, fast, informative, and relatively inexpensive diagnostic method to help determine anatomy, pathology and helping with diagnosis. As the number of contour plastic procedures increases every year [4], [5], US examination allows non-invasive diagnostics at different stages of treatment.

2.1.1 HA fillers usage overview

Today, injections of HA fillers are the gold standard of aesthetic medicine due to their features and low number of complications. To date, the use of hyaluronic acid-based fillers is one of the safest and fastest methods for solving aesthetic and some medical problems [4], [27].

Fillers based on HA consist of HA gel and basically its main function is to replenish the volume of tissues or skin depression. First of all, the effect of fillers is aimed at eliminating deep wrinkles, correcting the oval of the face, increasing the volume of the lips and even smoothing scar tissue [28].

Fillers based on hyaluronic acid are being used in aesthetics for contouring, biorevitalization and a number of other corrective and rejuvenating procedures in aesthetic medicine for rejuvenation and very often, as aesthetic patient's age is decreasing, for "beautification", and one of the most popular applications of HA is lip augmentation and/or correction of their shape, contour, wrinkles [5], [28].

In addition, HA injections ("beauty injections") may be performed on the following areas of the face and body: scars, wrinkles, deep nasolabial folds, uneven skin, dark circles under the eyes, adding volume to cheekbones, forehead wrinkes removal, scar treatments, post-acne scars filling, hands rejuvenation, replenishment of volume in cheeks, face oval correction, basically covering and offering solution for almost any patients request [4], [5], [28]. The effects are usually noticeable almost immediately. Biodegradation and filler natural dissolvement take from 6 to 24 months, depending on physical and chemical properties of HA used, such as concentration of HA and the density of the stabilizer [28].

The main advantages of using hyaluronic acid over other fillers are the absence of the need for an allergy test, the duration of the effect compared to other biodegradable fillers, the ability to use a dissolving antidote [27].

HA can be produced from various sources and the main one is bacterial, products of bacterial origin are the most common on the market, HA fillers of avian origin were previously common on the market, but today they are not available, although they had a good evidence base for use and according to a study from FDA found no difference between products of avian and bacterial origin [27].

In correlation with the increase in procedures performed, the number of undesirable complications also increases [6], [30], [31], [32], [33]. Complications might be divided into two categories: early or urgent (such as vascular compromise, inflammation) which occur during several days after injection and late (such as palpable nodules, oedema) which might develop after several month or even years after treatment [6], [7], [29], [30]. Although HA rarely causes allergy, immunological reactions can occur in the patient may arise or as a reaction to the stabilizing components in the preparation [27].

The main post-treatment reactions from HA fillers described in literature are pain syndrome, hematoma, oedema, indurations in injected area, nodules formation, inflammation, erythema, abscess formation, vascular embolism [25], [27], [28].

The overall incidence of inflammatory reactions is described in the literature and varies in different studies from 0.06% to 0.8%, it is important to note that in the studies all reactions occurring and disturbing after the procedure usually presented, however, 50% of post-procedural reactions are easily corrected or resolved themselves in less than 3 weeks, so the real risk of severe or late reactions is even lower, though it's hard to rule out the real incidence [27]. Using products with good clinical data is one of the best methods to decrease risk for any reactions after treatment and improve treatment outcomes for patient. Among the bacterial HA products, it is easy to distinguish and find good products due to good clinical data availability [27].

One of the most unpleasant and unfavourable outcomes after filler injections is a vascular complication. Research by world's leading doctors is focused to reducing the risk of developing acute situations associated with vascular occlusion, the search for effective ways to diagnose and treat them [6], [7]. The standard treatment is the introduction of medications containing the enzyme hyaluronidase [1], [27]. US usage might be beneficial, helping determine the location of the occlusion and the progress of the com

plication treatment [1], [6], [7], [29]. In medical literature, incidence of vascular complications is not detailed or accurately represented but is estimated to be 1:2000 to 1.10000, 0,05% to 0,01% respectively [34]. Schelke et al [34] conclude that frequency of vascular occlusion is 1:6558, making it 0,015% of estimated incidence risk and it is noted that even excellent professionals with significant experience might encounter this complication during their practice with a risk of 1:6558.

No data exists concerning complication frequency in Estonia. To date, there has been no consensus or decision about filler (or any other aesthetic treatment) complication reporting or diagnosing process [9]. The absence of any data concerning injectable fillers in Estonia, or any other European country (except Germany [9]) marks the need to create an epidemiological registry for performed cosmetic fillers and for registering complications. Present thesis will not cover this topic but signify the need of attention and research in this area.

New evidence-based recommendations for prevention and treatment of injectable fillers adverse effects from 2021 [6] provide suggestions for US usage for vasculature assessment, due to anatomy variability and post-treatment fillers identification, as US potentially might help with identification of previously administered fillers in case of late complications (oedema, fibrotic changes, inflammation, etc.) or before new filler injection.

2.2 Ultrasound

During impressive history of US usage in medicine, devices, technologies, and the areas of implementation of US have changed [35]. All US devices have a transducer and processor. The probe (transducer) generates a sound wave that penetrates body tissue [3]. The ability of human tissue to reflect ultrasonic waves is called echogenicity. The more liquid an organ or object contains, the darker it looks on the monitor, and vice versa. Liquid is rendered in black, while solid objects are rendered in white [36], [37], [35]. The principle of imaging is based on the acoustic resistance of body tissues. Having reached two tissues with different acoustic impedance, the beam of ultrasonic waves splits: one part of it continues to propagate in the new tissue, while the other part is reflected from it [3], [35], [36], [37], [38]. The reflection coefficient depends on the difference in the acoustic impedance values of adjacent tissues: the greater this difference, the greater the reflection and, of course, the greater the intensity of the recorded signal, which means the lighter and brighter it will look on the screen of the device (Ibid). The reflected sound waves picked up by the probe and directed to the processor, become transformed to the digital image [3]. US of the skin is performed on devices equipped with high-frequency sensors, higher than 15, or even 20 MHz [35], [36]. In traditional US examinations, in particular in aesthetic medicine, sensors of 3.0-12.0 MHz can be used [36]. For a special topographic study of the skin at the level of histological dissections, devices equipped with sensors of 20.0-25.0 MHz and even up to 100.0 MHz have recently been produced [39]. These devices are used exclusively in dermatological studies.

2.3 Ultrasound technology considerations

In recent time it has become possible to evaluate the structure of the soft tissues of the face in aesthetic medicine thanks to modern US machines with high-frequency sensors that can even evaluate the skin [36], [37]. US became more widely used in aesthetic medicine and dermatology with technology development and increase in the frequencies of the sensors and technology combinations (duplex US) [40], which made more detailed and precise research possible. In dermatology, doctors are using US for more superficial studies (dermis, epidermis) with high frequencies, diagnosing, monitoring, and determining normal and pathological conditions on skin, nail and hair, such as dermatologic emergencies, skin malignancies, skin tumours, inflammatory and infectious diseases, nail diseases, aesthetic complications [40], [41].

The visual determination of the depth of subcutaneous structures is not easy. Vascularization of every face is very variable and it's not always possible to reliably locate blood vessels even with greatest anatomical knowledge by textbook. The course of every facial vessel is very variable [6], [8]. Through US imaging before filler injection in the area of the intended work, it is possible to note the depth of the large vessels in relation to the face and planned treatment and take this into account during the procedure. It's more convenient to visualize vessels on the face and evaluating vascular flow using dopplerography [8], which provides information about the localization and depth of the vessels, the geometry of the vascular lumen, tortuosity, the presence of anatomical anomalies, and the thickness of the vascular wall [8]. Vessels painted in blue or red can be seen on the screen [40].

Compared to other research methods - computed (CT) and magnetic resonance imaging (MRI) - US seems more favourable to use due to the absence of background radiation and low cost [31], [14]. In addition, CT and MRI require complete rest of the patient, and US can be performed in any condition or position of the patient, in regular medical office without any specific equipment (Ibid). Compared to x-rays, US provides much more information, since soft tissues have little retention of x-rays. US as a non-invasive method of in vivo examination of soft tissues compares favourably with the ability to quantify skin and soft tissue structures; in the last 10-15 years, this type of study has been actively developed due to the emergence of high-frequency sensors (Ibid).

2.4 Current situation and development

The main pioneers in the use of US for aesthetic practice are cosmetic doctor and phlebologist dr Leonie Schelke and dermatologist dr Peter J. Velthuis, from Netherlands. Together they founded facial US training centre for health professionals in aesthetic without ultrasonography knowledge but developing professionally in order to delivering safe treatments and aesthetic outcomes for their patients [12], [19]. The name of the centre is Cutaneous and the trainings they launched raise the quality and safety for injectables with US [19].

Dr Schelke founded complications clinic for fillers years ago at The Erasmus University Medical Centre, helping patients with complications and collecting data on filler complications, whether they are patient- or product-related (inflammatory or allergic reaction) or procedure-related (misplacement of product). Together with dr Velthuis and research group from Erasmus University dr Schelke published several articles and proposals on filler complications management and usage of US in aesthetic medicine, promoting knowledge and safe practice [34]. Schelke and Velthuis, together with anatomy professor from Mayo Clinic College of Medicine and Science dr Cotofana took the initiative on „filler anatomy “ [12], focusing in their message on the fact that cadaver or surgical anatomy, or any other anatomical instruction may vary and differ from individual anatomy and US imaging of the face structures.

Developer and explorer of dermatological US dr Ximena Wortsman, radiologist from Chile, who advocates the support and improvement of dermatological US performance. With the initiative of dr Wortsman, an international working group was created for supporting standardization of performing dermatologic US examinations [42]. The working group compose of 13 physicians who have been working on a regular basis and publishing in peer-reviewed articles on dermatologic US [42]. They came up with conclusion and initiative to standardize the performance and quality of dermatologic US examination, to ensure the quality and proper use of the technique, through health professionals proper training and creating the standardized report of the US examination that should be recorded in a proper way and attached to the patient health record [42]. One potential limitation with this initiative in terms of given research is that it is focused only on the skin examination (dermatological), but usually dermal fillers such as HA are placed deeper than skin layer – periosteum, hypodermis. As observed and noted by Wortsman [14] term „dermal fillers” might be incorrect, as US confirms that usually HA appears deeper than skin.

Also, Wortsman proposes [14] that US in terms of fillers might be used not only for treatment or safety improvement, but also for studying and testing the longevity and anatomic effects of cosmetic fillers, as histologic analysis may be limited due to deep placement of the filler. This might make potentially significant positive contribution into fillers research, as in general it is a quite short-lived medical device on the market (a bit more than 20 years) and due to massive usage [4], [5] and enormous offer of different fillers on the market, an independent method of control and evaluation of the filler might give supplemental and complementary information of assessment.

In international recommendations for the treatment and prevention of complications, US is mentioned for the first time in 2021 [6]. Before that, studies dated 2016 and 2018 [7] [43] focused on complication and prevention and management research, provide traditional and conservative recommendations such as aspiration, anatomy knowledge, palpation, avoiding dangerous zones. Jones et al [6] in 2021 provides modern evidence-based recommendations for prevention and treatment of injectable fillers adverse effects, proposing US usage for vasculature assessment, due to anatomy variability and post-treatment fillers identification.

3 Methodology

3.1 Overview of research design

The state-of-the-art review method [44] is considered to be suitable method to achieve the aim of the research because it will allow to find the most current research concerning given area and thus will reflect the highest degree of development in the field. State-of-the-art review intents to address more current issues as opposed to other combined retrospective and current approaches, based on comprehensive search of the current literature [44]. There are no official guidelines for state-of-the-art method, thus given methodological guideline used in this study is an adjustment on Khan et al [45] of systematic reviews.

To perform the state-of-the-art review the method of conducting systematic reviews was approached and four out of five steps of systematic reviews described by Khan et al [45] were followed: 1. Framing questions for the review; 2. Identifying relevant work (identifying and selecting relevant studies); 3. Summarizing the evidence; 4. Interpreting the findings. Khan et al [45] suggest quality assessment to every step of a review, as detailed quality assessments show heterogeneity of included studies and outcomes regarding the suitability of the results, aditionally, quality assessment verify the validity of findings and provide recommendations for future research. Even though Khan et al [45] suggest that quality assessment is essential, Grant et al [44] claims that there is no need for formal quality assessment in state-of-the-art review thus the step was disregarded for the thesis and only few aspects that can be regarded as quality issues were extracted and included for the summary. These aspects were author's occupation, source (journal) and study design. And they were included in order to detect and reflect on possible bias and evidence appraisal of the included studies, and also acknowledging limitations appearing in given study.

As a method state-of the-art intend to review most up-to-date information and outline development and advancements in the given field of interest, thus all studies including case reports were included due to importance of every detail of information and proposed innovation or observation.

According to the research problem and proposed research questions, it is relevant to provide thorough search of the comprehensive literature that has been produced in the last decade, especially to show the evolvement and maturity of the field. A synthesis of state-of-the-art thinking will allow to evaluate the usefulness of US. Moreover, state-of-the-art review has a potential to discover new perspectives or trends for further research recommendations [44].

Other literature review methods were considered such as rapid, scoping, systematic and critical but these turned out to be inapplicable for various reasons like time and resource constraints or too narrow of focus of the possible method. As the researched topic is a very much new trend [3], [15], [16] and not very implemented into routine practice in aesthetic medicine yet the main consideration was scoping or state-of-the-art methods. After evaluation of the thesis's objectives, research questions the state-of-the-art method was chosen because it would allow to answer research questions three and four as well, not only give an overview of the field. Moreover, usually, in scoping reviews, the critical view on the quality level of studies is not performed [44].

State-of-the-art reviews provides significant value for newcomers to the field, highlighting most up-to-date information and finding opportunities for further research. State-of-the-art provides valuable amount of information about development and advancements in the given field of interest [44]. For visualization of the literature review, the 2020 PRISMA flowchart [46] was used.

Main steps for the review [45]*:*

1. Framing questions for the review
2. Identifying relevant work (identifying and selecting relevant studies)
3. Summarizing the evidence
4. Interpreting the findings

Even though according to Grant et al [44] there is no need for formal quality assessment in terms of critical appraisal of the studies to be analysed and included to the state-of-the-art review it was included with an attempt to provide trustworthy and reliable outcome. To achieve reflection on the rigor (accuracy) in present research it's important to acknowledge the measures to establish and assure validity and reliability.

3.2 Framing questions for the review

Though US is a well-researched visualization method, its implementation to aesthetic medicine is complex and challenging, raising many questions. Research questions of this thesis reflect main concerns about US perspectives in aesthetics, covering two main indeterminacies: the technology influence and research quality, as well as technology evolvement. Concluding these five research questions consisted of multiple iterations. After defining authors personal interest and lack of knowledge, the thesis's aim and objectives were set and rephrased many times and reviewed by the supervisor and the thesis committee members as well.

3.3 Identifying and selecting relevant studies

A search of the literature exploring the new possibilities for the use of US in aesthetic medicine was carried out. The search was conducted according to PRISMA 2020 guidelines [46] in three medical electronic databases. Embase and Science Direct was used for extensive list of peer-reviewed journals, articles of aesthetic dermatology, cosmetic disciplines, dermatology, plastic surgery. Additionally, PubMed was used for including Medline and additional biomedical content. The time frame of the study was not carried out, although due to the novelty of the topic under study, only the most recent studies are naturally present in this area. As researched topic is an innovative and developing area of aesthetic medicine, all studies including case reports were selected due to importance of every detail of information and proposed innovation or observation. The keywords used for the research:

- Mesh - „Dermal fillers" or „hyaluronic acid" or/combined with „ultrasonography" or „doppler "
- Keywords - „Ultrasound" combined/or „cosmetic fillers" or „plastic surgery" or „aesthetic medicine" or „aesthetic dermatology" or „dermatology "

Records identified through database searches (n=1223) were collected to Zotero, a reference management software, for subsequent collection and thorough management of bibliographic data: duplicates removal, citation, sample selection and organization.

The selection of full-text sources was carried out after abstract screening. Full-text articles assessed for eligibility were evaluated for relevance, authority and accuracy, to cover the researched topic precisely.

In addition, the bibliography of the selected publications was examined in order to find additional materials for better reflection the topic under study and better background research.

All data for research and full texts were obtained in January 2022 by author exclusively.

3.3.1 Inclusion and exclusion criteria

The main reason for excluding articles was limited amount of relevant information. Many articles were misleading or included insignificant part of information related to the topic. Inclusion and exclusion criteria are presented in Table 1.

Included data reflects US usage in anatomy assessment for safe treatment, complication incidence overview and the necessity of safety improvement, hyaluronic acid detection in the tissue, filler complications diagnosing and managing with ultrasonography, as well as research and development data of US technology in aesthetics. Information about US evaluation of vascular and soft tissue peculiarity, which helped the author to prove the statement about usefulness of US in aesthetics, especially in dangerous zones, was also collected.

To ensure that studies and findings are not influenced by commercial interest of providers it was decided to exclude any supported or funded studies during the study selection process.

Eligibility criteria	Study covering diagnostic US usage in / or related to aesthetic medicine on healthy humans.
Criteria for evaluating included articles	• Relevance: the relevance of the content and its coverage of the research objectives. Only aesthetic medicine articles included US for dermatology or plastic surgery were excluded due to insignificance. *(Reason 1)* • Authority: what is the source of information and is the study design clearly defined and consistent with the objectives of the study. Peer-reviewed and non-sponsored articles were searched. • Accuracy: is the study reliable, correct and has enough data for trustworthy conclusions. Even one patient case reports were carefully included due to importance of every detail of information.
Inclusion criteria for full-text article screening	Articles of US reflecting subdermal on-label usage of hyaluronic acid as a filler for aesthetic indications, in vivo, on humans and anatomy examined with US in the region of face and hands on live humans were used. Cadaver anatomy investigations were excluded. *(Reason 2)* Regular skin or soft tissue measuring or improving techniques were excluded. *(Reason 3)*
Type of study	All kinds included.
Language	Only English.
Timeline	Any

Table 1. Inclusion and exclusion criteria

3.3.2 Data extraction

For data synthesis the following data was mapped: authors (as some authors report that their studies are not sponsored, they might be involved in some projects that may can influence their opinion, and it is possible to identificate them by name), publication, involved operators' specialization, participants characteristics, interventions and settings, study design, aim, year, measurement tool, outcome, key conclusion.

3.4 Summarizing the evidence

Khan et al (2003) suggest that „data synthesis consists of tabulation of study characteristics, quality and effects as well as use of statistical methods for exploring differences between studies and combining their effects (meta-analysis)“ [45].

In given study to perform data synthesis study characteristics, quality and effects were tabulated. Meta-analysis was used to statistically combine data from different studies into a summary (operators' specialization, objectives, apparatus, journals). Data selected from each study was collected to Microsoft Excel and included: names of the authors; publication; aim of the study; study design; characteristics of participants; intervention and setting; measurement tool and indicators; outcome; key conclusions, involved operators' specialization. In the presented review, summary statistics and results of meta-analysis is presented in figures and tables and comlementally explained narratively, with narrative approach study encompasses state-of-the-art data, insights, concepts and provider perspectives. To draw the findings from different studies together, findings were summarized by themes and interpreted.

3.5 Interpreting the findings

According to Grant et al [44] the purpose of state-of-the-art is to present in a narrative manner most current knowledge if the researched field and find priorities for future investigations and finding new prospects. To cover several research perspectives posted in research questions, the study results will be presented in five categories according to raised research questions. Data collected from research papers according to the scope of the study presented by using descriptive quotes.

Studies were linked, analysed and compared to each other according to categories as stated by field or method of application, study outcomes, authors expertise. Findings of given research were related and compared with evidence-based studies and knowledge to indicate reliability and nature of alignments.

3.6 Ethical aspects

The review method in given thesis determines the use of secondary data and thus no ethical approval was necessary. No intentional plagiarism or other original creations usage was

applied, legitimate citations of used materials are carefully provided. US usage in aesthetic medicine is an innovation and author urge to acknowledge that given research present information and perspectives that need to be confirmed by large-scale studies with large cohorts and any examinations or examination interpretations need to be provided by trained professionals, who can ensure patient safety.

Nevertheless, given topic is a part of continuous development of niche medical field and author encourages all health professionals involved in aesthetics to endeavour and contribute into any methods developing safety, through education or participation in scientific research.

4 Results

47 articles published between 2008 and 2021 were included in the study and categorized according to the clinical field of application or implementation. List of included studies is presented in Appendix 1.

The PRISMA flow diagram [46] on Figure 1 maps out the study selection process, number of records identified, included and excluded. Reasons for exclusion are presented above.

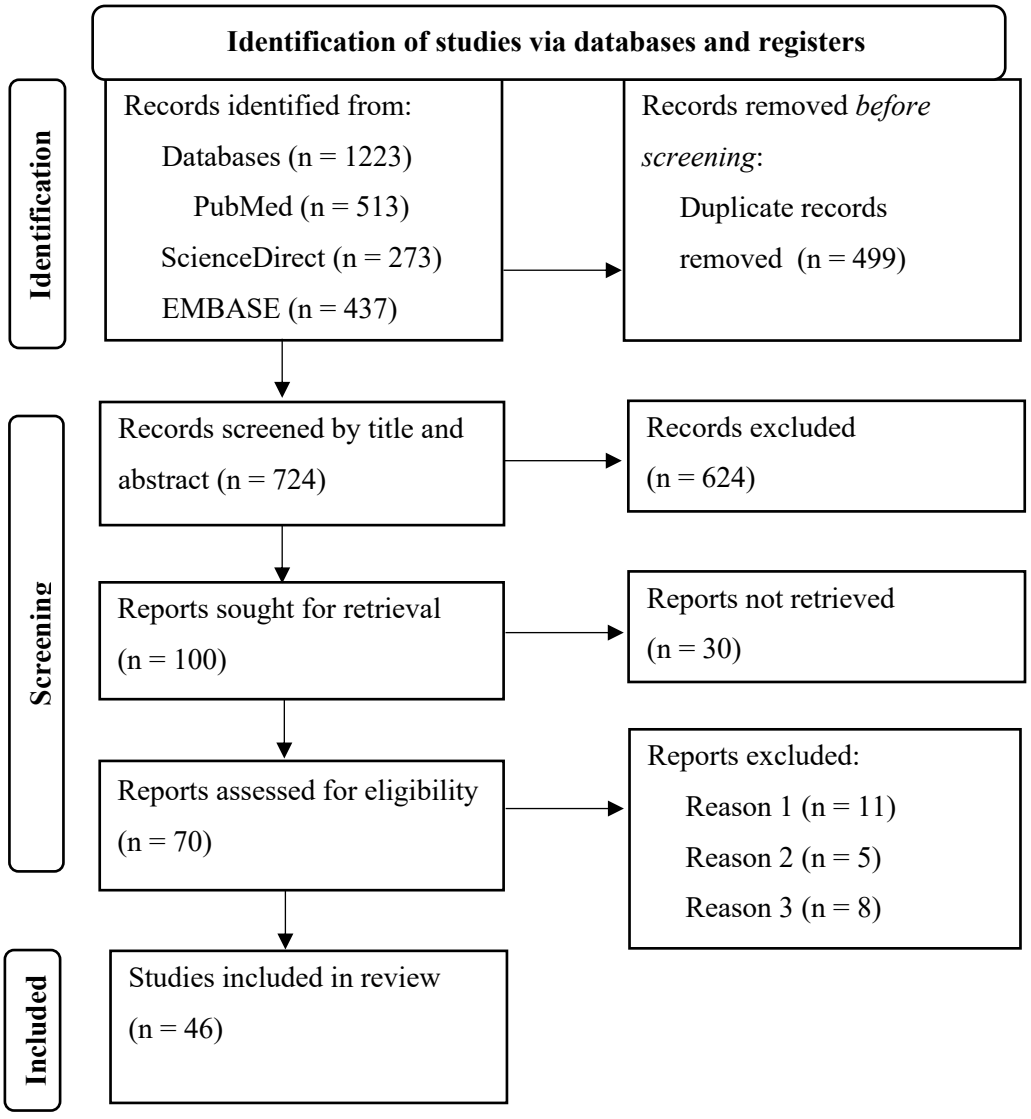

Figure 1. Flow and selection of studies in PRISMA diagram.

Half of these articles (n=24, 51%) are dated 2020 and 2021 and reflect the most current situation in the field. 12 studies outline the role of US for complication management, [13], [20],

[14], [32], [47], [48], [49], [50], [51], [52], [53], [54], 14 on post-procedural filler assessment [2], [3], [14], [20], [22], [25], [55], [56], [57], [58], [59], [60], [61], [62] and 12 on analysis of anatomical features [3], [18], [31], [54], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72].

The results will be presented under the following five headings, according to research questions and the scope of the study:

1. Evolvement of US usage in aesthetic medicine.
2. Main types of US used in aesthetic medicine.
3. Applications and indications for US examination in aesthetic medicine.
4. Usefulness of US technology in terms of improving the usage of HA injectables.
5. Main requirements for providing proper US examination in aesthetic medicine.

4.1 Included studies overview

Study design of the included papers almost 1:1 compose retrospective and prospective studies, n=20 and n=22 respectively. Review papers (n=5) in given study present generally summarized recommendations, guidance and instructions for US usage [15], [16], [17], [14]. Study design of the included papers is presented in Figure 2.

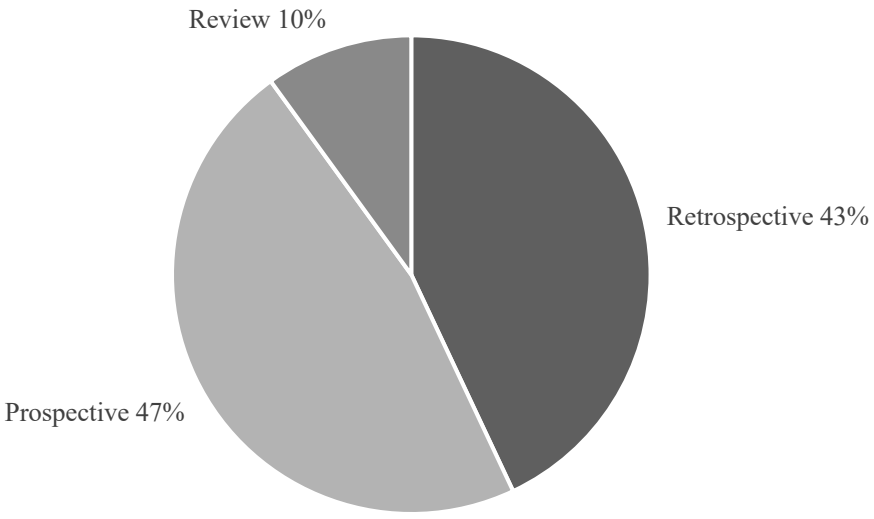

Figure 2. Study design of the included papers

Prospective studies include mostly healthy volunteers, who underwent filler procedures during with US guidance study or were examined or scanned using US imaging for facial anatomy investigation. Some studies provide sonographic examination results by blinded investigator,

for unbiased outcome [73]. For prospective studies outcomes are mostly presented with quantitative data obtained from clinical results [4], [30], [55], [58], [67], [75] e.g., measurements of arteries or other anatomic information, detection of cannula during treatment and blood vessels.

Retrospective studies investigate patients with a history of facial fillers for overall product condition observation in soft tissues or complication treatment manipulations control and management. Outcome assessment of retrospective findings is primarily presented in detailed information, e.g., exact location of filler, measurements of blood vessels, diagnosis with a detailed description of US appearance [13], [48], [51], [59], [61].

Studies about the use of US are presented in various journals from the field of dermatology, plastic surgery, aesthetic medicine and others. The distribution of included studies throughout journals is presented in Figure 3.

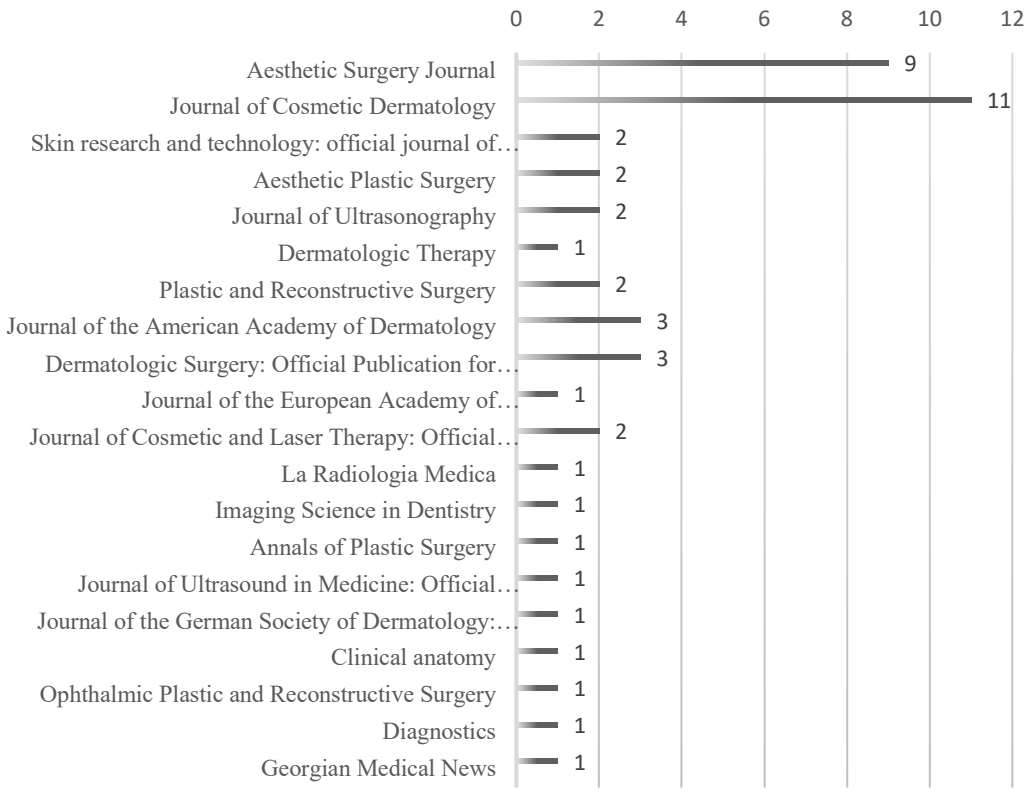

Figure 3. The distribution of included studies throughout journals.

11 studies have been presented in Journal of Cosmetic Dermatology, which's impact score is 2,36 and h-index is 44. The Aesthetic Surgery Journal present 9 included studies, and journal's impact score is 1,87 and h-index is 58. Impact score and h-index of all journals of included papers is presented in Appendix 2.

4.2 Evolvement of US usage in aesthetic medicine

Given study presents works from 2008 to 2021. There has been a significant increase in research since 2019. Studies before 2018 research and report exclusively the assessment of injectable dermal fillers, several studies [2], [14], [55], [49] describe fillers detection and identification methods with US and its application. Some studies present filler sonography usefulness considerations [21], [22], [62], [73].

Doppler US usage is reported in 2018 for the first time by Shelke et al [3] for safety improvement with Doppler vascular mapping and by Tansatit et al [63] for forehead arteries investigation. Since then, starting from 2019 research amount is increased from 4 to 12, and 71% of studies are focused on identification of facial fillers with Doppler (e.g., Duplex US) before, during and after filler injections. 29% of studies explore US assessment perspectives, soft tissue anatomy and filler materials assessment.

The number of published research papers on US application for aesthetics and distribution throughout the years are presented in Figure 4.

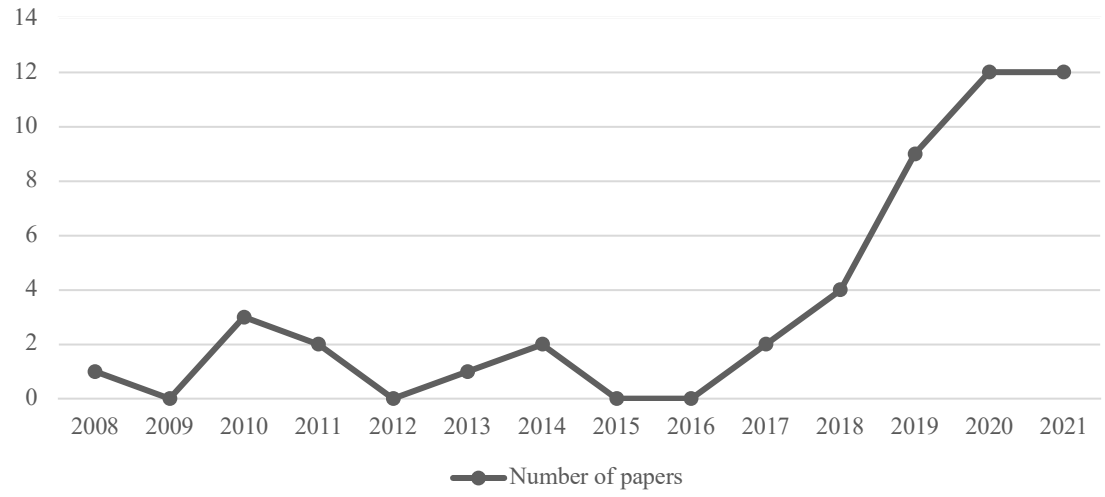

Figure 4. Number of published research papers on US application for aesthetics and distribution throughout the years.

4.3 Main types of US used in aesthetic medicine

An analysis of the literature shows that for aesthetic indications, US with transducer readings of 7-22 MHz was mainly used [14], [68], in B-mode, also in Doppler or duplex mode [13], [16], [17], [20], [47], [53], [54], [68], [69]. Di Santolo et al [53] claims that 5-17 MHz are

mainly used for normal or pathological skin conditions. Frequency of over 15 MHz is described by Di Santolo et al [53] and Mlosek et al [48] as innovative and appliable for very superficial skin examination, such as epidermis, dermis or deeper tissues.

23 of included studies are focused on fillers or anatomy assessment in soft tissues with B-mode examination; 18 of studies assess the perfusion in blood vessels with Doppler; 5 studies provide simultaneous Duplex examination.

US types used in included studies are presented in Figure 5.

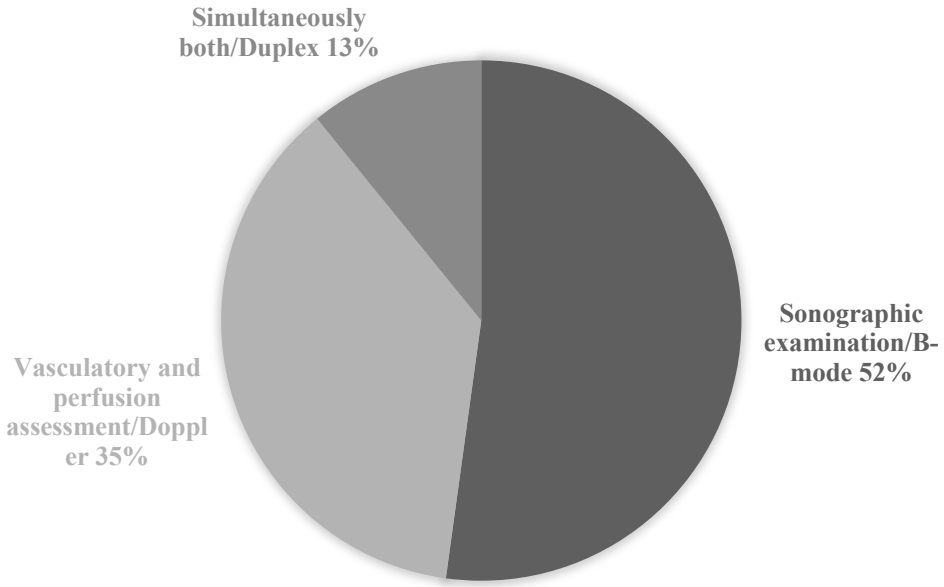

Figure 5. US types used in included studies.

B-mode sonography studies aims are focused on several objectives and presented in Figure 6.

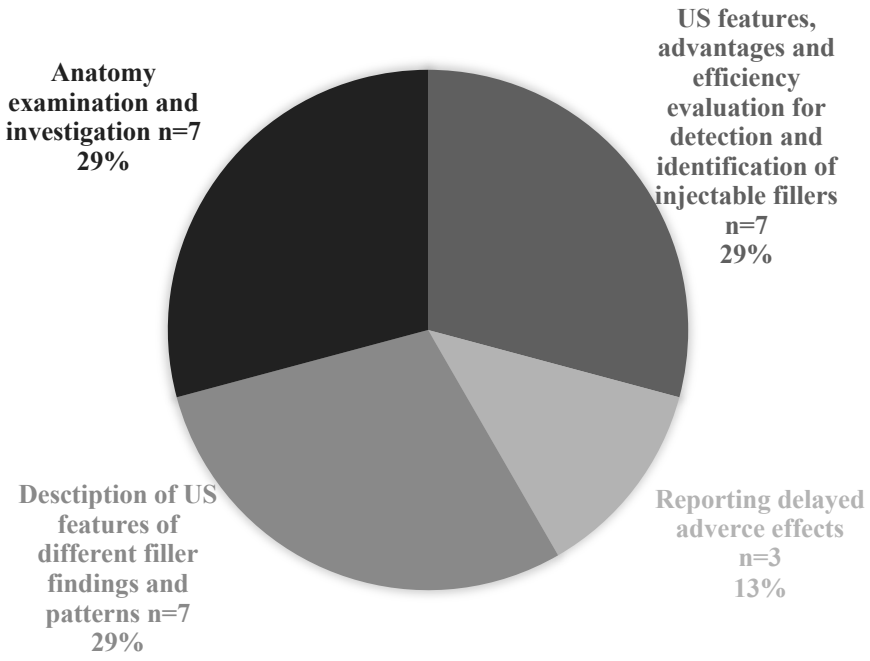

Figure 6. B-mode sonography research objectives in included studies

Doppler sonography studies aims are focused on several objectives and presented in Figure 7.

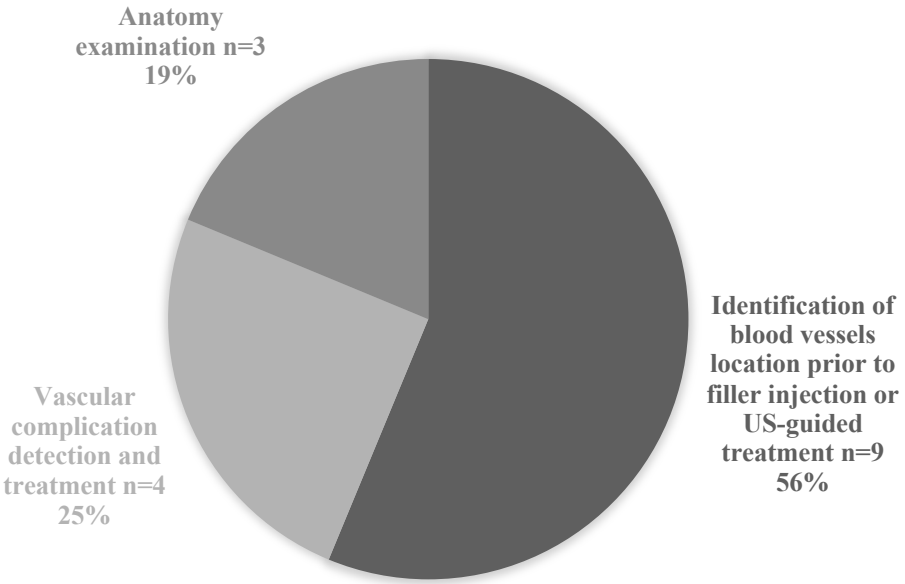

Figure 7. Doppler sonography research objectives in included studies.

Duplex sonography studies aims are focused on two objectives: pre-treatment examination (n=2) and assessment and management of complications (n=4).

According to different studies Doppler US usage may be very helpful and informative to provide information about blood vessels to avoid complications [18], [65], [68], [70], [74],

[75]. Mlosek et al [61]suggest, that under Doppler examination would pe possible to visualize if the blood vessel is blocked or pressed, if the lack of blood flow is observed.

High-frequency US, up to 22mhz [22], [55], [52] is described as very efficient in providing clear information about fillers on US image. Average and conventional measurements that are presented in studies are 7-18 MHz [2], [21], [48], [53], [62], [73], allowing to identification the location, nature and amount of the fillers [2], [22], [49], [21]. Schelke et al [21] suggests, that resolutions between 13 and 20 mhz may be more accurate for fillers examination and identification in the different layers of the skin or deeper soft tissues.

In 2 studies authors present advantages of Duplex (combined) US [13], [32]. Authors conclude that Duplex technology might be the most favourable due to providing the essential anatomy information (also detecting fillers) and vascular mapping at the same time, also easier and more distinct to use. When the Doppler system is integrated with US, the device is named Duplex [3]. Duplex US technology is highly promoted on European aesthetic market, as it appears to be very useable and useful [13]. Usage of Doppler US in order to identifying large blood vessels might potentially help to avoid course of the vessels found and increase safety to the treatment [3], [8].

4.4 Applications and indications for US examination in aesthetic medicine

The findings show that US in aesthetics is employed mainly for:

- Facial assessment and anatomy determination: vascular mapping, fat pads, muscles and US -guided procedures.
- Evaluation and identification of previously placed fillers: location and composition.
- Vascular emergency.

17 studies presented in given research are focused on exploring the ability of US to determine individual anatomy [63], [64], [66], [69], [70], [72], [71], [75], [76], [77], such as finding blood vessels and examining soft tissue structures, as well as US-guided procedures are described [75], [78], highlighting the ability to inject fillers into “dangerous” zones with large blood vessels more safely [3], [18], [31], [54], [68]. The ability to evaluate blood flow in real time opens new prospects for the use of US in aesthetic medicine, different authors suggest that US-guided injections may become a new standard in procedures in the future [18], [68], [75]. US

allows to evaluate and determine the blood supply into tissues and face areas at different stages of the procedure: vascular mapping before injection, US-guided procedure [18], [65], [75], [74], [76], [78] follow-up control or complication examination/management [18], [20], [47], [54], [68]. Also, some studies show the ability to assess the condition of previously located fillers, their location and composition to avoid unfavourable reactions [47], [54], [68].

4.4.1 Facial assessment and anatomy determination: vascular mapping, fat pads, muscles, and ultrasound-guided procedures

Gerber et al [33] in clinical letter from 2019 report their experience with pocket Doppler US in order to identify the location of blood vessels, proposing Doppler as a useful method for detecting facial blood vessels prior to filler injections. Mespreuve et al [31] describing visualization techniques of the facial arteries notes, that with US may be possible to identify or locate single blood vessels, but for visualization of complete 3D arterial network of the face MRA (magnetic resonance angiography) would ideally be the method of choice, however recognizing high cost and several procedural disadvantages. Concerning US Mespreuve et al [31] claims that Doppler analysis may be useful to facilitate the visualisation of a small area or specific vessels, however noting that US technique in very operator depending, and might be very time-consuming. Velthius et al [16], [17] provide detailed guide to Doppler US analysis in all face areas separately, describing standard US transducer positions in the face, claiming that in these positions fixed anatomic structures can be found easily. Among others, Velthius et al notes that vascular mapping may increase safety and presume, that sonographic examinations will become as normal in aesthetic medicine as it is in phlebology.

Several explorative studies investigated and analysed the anatomy of face vessels on different face areas:

- on the forehead for supratrochlear, supraorbital and superficial temporal arteries [63], [66], [77], exploring the arterial anastomosis and the change of plane of arteries. Park et al [77] in their study also report the veins in the forehead midline precisely indicating their findings and specify vessel's locations, highlighting the fact that glabella region is a high-risk zone on a face.
- on the nose for nasal area vessels. In their study Moon et al [69] report precise location of intercranial vein and dorsal nasal artery according to their study results, in conclusion

authors share recommendations for performing nose filler augmentations according to their findings, in terms of prevention of vascular embolism.

- Ten et al [70] investigating nasolabial folds area on the face with US for examining and observing of angular artery and facial artery course concludes in their study, that there is no completely safe depth or region for nasolabial filler injection, and new filler injection strategies are needed for this region.
- Lips for superior and inferior labial arteries [64], [71]. Cotofana et al [64] present results showing that position of the labial arteries may vary and propose more superficial injection technique. Similar findings were obtained by Lee et al [71] also report precisely different location of the arteries in the lips and suggest superficial approach for lip augmentation, withal noting that US- guided injections would minimize the possibility of complications and provide safety and efficiency.
- Schelke et al [67] present study results that provide valuable insight about the mobility of the superficial and deep midfacial fat compartments. According to Schelke et al study's results contribute in several ways to understanding of the deep supraperiosteal approach of injection techniques in the midface.

All authors [63], [64], [66], [67], [71], [69], [70], [77] presenting US evaluation results for face anatomy note that US allows to provide reliable and clinically relevant information to perform safer procedures and ensure safety, thus avoiding the occurrence of vascular complications. Lee [68] in her study conclude, that Doppler device usage is affordable and easy to use, and the usage of this device in working routine might be considered, thus noting, that more data needs to be collected and reviewed about the benefits of this tool in terms of improving safety.

The role of US in the planning of facial contouring was studied, various forms of complications were investigated: urgent and delayed, as well as the prospects for their treatment. The high efficiency of US in determining the nature of changes in tissues after injections of fillers based on HA are presented in studies [2], [21], [22], [26], [55], [49], [73], [14], [56], [58], [62] as well as other fillers such as calcium hydroxyapatite, permanent fillers [2], [21], [22], [26], [14], [55], [62], [58], [73] etc., helping with distinction between different materials.

The role and impact of US -guided injection treatments is described in detail in several studies [46], [56], [57], [74], [78], [75], covering particularly well researched areas – tear-trough [56], [57], glabella [46], [75] and nasolabial folds [78], in general all presented studies conclude, that under the guidance of US device it is possible to perform treatments more safely, to inject

info accurate anatomic layer and avoid intravascular infusion. Iwayama et al [78] conclude that US -guided method for nasolabial fold was effective and ensured the safe injection of an HA filler for the high-risk area. De Pasquale et al [57] describe their technique for tear-through treatment and acknowledge the effectiveness of high-frequency diagnostic US in the assessment of dermal filler longevity, noting that it was always possible to measure and identify the injected filler for sonographer. As noted by Lee et al [46] glabella is one of the most dangerous locations for filler injection, causing necrosis or possible visual complications, demonstrating in their study that Doppler US can be used to confirm the location of the supratrochlear artery before filler injection, that helps to avoid vascular complications. Likewise, Teixeira et al [75] propose and describe US -guided filling as a part of injectors routine, to prevent serious complications like necrosis and blindness.

Moreover, recently a thorough description of a safe doppler US guided technique for HA filler in the face was presented and described by Rocha et al [18] in the end of 2021. In this study a Doppler US -guided injection technique is presented in three steps: arterial, mapping, real-time US -guided filling, and evaluation of injected filler. In the results authors report the greater safety against vascular occlusion and suggest adopting described method into professional routine of injectors. Also, authors conclude, that in the future US -guided technique may become mandatory for healthcare professionals who work with HA injectables, to ensure safety for patients and legal protection for professionals.

4.4.2 Evaluation and identification of previously placed fillers: location and composition

12 of presented publications are focused on the results of comparing US with the chemical nature of fillers and diagnosing complications after their introduction [3], [47], [49], [52], [54]. The studies describe the examination of fillers and complications using US and MRI, soft tissue analysis and treatment tactics, proposed and implemented: mainly conservative or the introduction of the enzyme hyaluronidase with the help of US control [3]. Monitoring of the process and outcome of treatment was also carried out using US. Studies [48], [53] show that in more than 95 percent of cases, US can locate and characterize complications, often showing asymptomatic granulomas and inflammation, filler migration and resorption. US is effective not only in the diagnosis and determination of complications but is also used for the introduction of the hyaluronidase enzyme under US navigation, for the most precise injection into the bolus of ineligible filler [13], [32], [47]. There are studies showing, that with the urgent

administration of hyaluronidase, the risk of tissue necrosis can be prevented, US helps to precisely determine the problematic area for a timely response [13], [32].

Concerning sonographic parameters and identification of late complications - two studies describe and offer nomenclature recommendations for describing the structures found on US [15], [48]. Typical US signs of HA are described at different times of administration: immediately after procedure and after some time [21], [56], [57], [58], [59], [60]. It is noted that US allows visualizing the filler and tissues around it, later control allows to determine asymptomatic reactions (inflammation, etc.) in the tissues [2], [21], [22], [26], [14], [58], [62], [73].

HA fillers are claimed [73] to be recognizable on US as different fillers generate different patterns of echogenicity. Mainly HA visualization on US is described as anechoic or hypoechoic due to hydrophilic properties [13], [15], [14]. Schelke et al [3] declare HA to appear anechoic or hypoechoic on US findings, due to HA hydrophilicity, as HA acid bind water into injected area and water content does not reflect sound waves.

Wortsman et al describe in two studies [2], [14] use of US for facial fillers identification and detection, showing that with the help of US it is possible to identify fillers *in situ* to determine the exact location of the filler, the size, abnormal positioning, and blood flow measuring. In cooperation with Schelke, Wortsman et al [15] present nomenclature proposal for the sonographic description of injectable fillers. In this study different US findings are described according to different filler materials. In their study Schelke et al [15] describe HA acid as "well defined oval- or round-shaped anechoic homogenous deposits without any signs on internal echoes". Though Urdiales-Galves et al [26] argues, that these findings are probable immediately after injection, later fully integrated HA fillers present heterogeneous US pattern similar to healthy skin or subcutaneous cellular tissue.

According to Grippaudo et al [62] it is possible sonographic assessment of dermal fillers is possible in 97,5% cases, and in another study by Grippaudo et al [73] sonographic identification and localization was possible in 100% cases. Similarly, to other previously mentioned research, Grippaudo et al [62], [73] present detailed description to their findings, demonstrating distinct difference in in sonographic patterns of different injectable fillers (e.g., hyaluronic acid, silicones, calcium hydroxyapatite etc). Similar results were obtained by di

Santolo [53] and Mlosek et al [48] reporting 97% and 100% (respectively) of cases identified and described.

Several studies focus their research on assessment, clinical efficacy and evaluation of integration of HA fillers [56], investigation of the distribution patterns [58], [59], [79], evaluation modality of side effects [48], [49], [51], [61]. Authors [55], [58], [59], [61] conclude, that data obtained with instrumental method (US) helped to understand the mechanisms of action of the injected HA, consequently confirming, that these results highlight the value and reliability of ultrasonography as an instrumental method of evaluation.

4.4.3 Vascular emergency

Shelke et al [32] present very detailed study concerning vascular emergency early US diagnosis. This study provides valuable insights into the utility and useability of US in duplex mode for urgent vascular complications. The main focus of Schelke et al work is on hyaluronidase administration protocol description under US guidance, as noted by authors, if treated in time it is possible with "one single hyaluronidase injection into filler deposit to prevent skin necrosis". According to given study, US is used in order to better understanding of affected (compromised with filler) blood vessel location, for precise hyaluronidase administration. Authors provide valuable and significant contribution into vascular emergency management, providing important knowledge about important US findings appearing immediately after HA filler injection and hyaluronidase usage protocols.

In her letter from 2020 to Dermatologic Therapy Journal editor, Schelke [13] suggests, that the use of duplex US may improve the safe of injectable fillers and also may become important part of complication management protocol, anew mentioning that intralesional injection of hyaluronidase with US guidance ensure treatment accuracy.

Similar observation and suggestion are provided by Kwon et al [47], reporting the case study and professional experience, that if early signs of vascular compromise are observed, hyaluronidase injection under US guidance is very reliable method for complication treatment.

One study [20] separately describes Laser Doppler skin imaging for vascular complication treatment after filler injections. Given tool is technologically different from US, but in their study Lee et al [20] provide valuable information concerning superficial microcirculatory perfusion in the skin for locating ischemic zones caused by injectables, and name this method

fast, easy, and reliable. Authors also suggest this tool for damaged area determination for hyaluronidase treatment. Though given study provides effective outcomes, authors note the necessity for large-scale studies with large cohorts.

4.5 Usefulness of US technology in terms of improving the usage of HA injectables

US for aesthetics is described [3], [22], [32] as non-invasive, painless, fast and useful imaging method for assessing the effects of injectables. The ability to assess blood flow in real time opens up new prospects for the use of US [3], [17], [54] for potentially safer injectable treatment outcomes. Schelke et al [21] state that US examination may give useful information about localization, migration, or degradation, providing significant information also for clinical research and improving safety.

Majority of the studies involved in research conclude, that US examination provides reliable support for the detection, localization, identification and evaluation of face structures or fillers in tissues before or after treatment. Velthius et al [16], [17] observes, that US is being promoted in aesthetics as a first line imaging technique, founding that the course, the depth and distribution of the arteries may vary from expected, the injection projection may be adjusted accordingly with the help of US visualization. Similarly, Wortsman [14] suggests that" to date, sonography is the first-line imaging modality for dealing with cosmetic fillers". Di Santolo et al [53] outline ultrasonography as precise and detailed method, noting that its non-invasive value helps to avoid invasive procedures such as biopsy.

Velthius et al [17] raise up ethical component, observing, that when it is proved that US examination may prevent filler complications or provide safer outcomes, healthcare professionals will be obliged to use US devices.

Several studies [13], [20], [22], [51], [48], [61], [68] describe their limitations as insufficient number of patients examined is included into the study to draw accurate conclusions about US efficiency in filler complication management, however authors acknowledge that US provided significant impact to the result of patients in their study and propose solid large-scale studies to confirm alleged results [20].

Schelke et al [3], [15], [21] evaluated the possibility and effects of post-procedural US implementation, suggesting nomenclature terminology and parameters for soft tissue filler description. Schelke et al [21] indicating, that more data to confirm filler echo densities is needed.

Only one group of researchers presented a guide for US usage and application, with profound overview of the technique and main principles of the technology and sonographic anatomy [16], [17]. Researchers from the same group also present several proposals and initiatives on US description, reporting effective usage [15], [14], [48]. The main parameters to be described for fillers US reporting are echogenicity, texture, border, shape, diameter, quantity, internal characteristics, artifacts, anatomical location and evolution [15].

The role of US in the planning of facial contouring was studied, various forms of complications were investigated: urgent and delayed, as well as the prospects for their treatment. The high efficiency of US in determining the nature of changes in tissues after injections of fillers based on HA are presented in studies [49] [73] [22] [14] [58] [55] [26] [2] [56] [62] as well as other fillers such as calcium hydroxyapatite, permanent fillers [2], [21], [22], [26], [14], [55], [58], [62], [73] etc., helping with distinction between different materials.

In the evaluation of the role and utility of US usage in aesthetics Schelke et al [3], [15], [21], [32], Grippaudo et al [62], [73] Wortsman et al [2], [14], Young et al [22] and Mlozek et al [48] emphasize and draw attention to the usefulness and advantages of this method.

Wortsman [14] conducted evaluation of different methods for fillers identification, such as US, MRI, CT, concluding that sonography is the first choice for filler identification and assessment. Moreover, Wortsman et al [2] outline US in other study as useful and convenient method fillers evaluation, observing, that US may assist in prevention of harmful effects from other imaging methods such as MRI, CT, PET/CT. Mlozek et al [48] also draws attention to limitations of MRI imaging application for filler assessment, such as high cost, procedure duration and limited access, suggesting US as non-invasive, safe, inexpensive, usable and easily available. Di Santolo et al [53] reaffirm same observations, noting that to perform trustworthy results sonography expert involvement is needed.

However, Schelke et al [3], [21] and Velthius et al [17] suggest that US (preferably Duplex) should be available in any aesthetic clinic providing injectable treatments, though mentioning, that good understanding, skills and knowledge are necessary for US examination [21] and

„time and money “should be invested when US usage is being implemented into practice” [17]. Velthius et al [17] declare the belief, that over time US examination will be a part of routine and normal usage in aesthetic medicine.

4.6 Main requirements for conducting correct US examination in aesthetics.

US operator and experience is a relevant topic to be reviewed. Di Santolo et al [53] suggest that US examination should be provided by doctors with sonographic (and aesthetic) experience. In the current research 75% (n=35) of all studies were provided by or in cooperation with radiologists, 15% (n=7) provided independently by dermatologists, 9% (n=4) provided by surgeons and 2% (n=1) by ophthalmologists. Operators’ specialization in all included studies is presented in Figure 8.

It is notable that before 2019 researches were provided mostly by radiologists (or with radiologists involved for result interpretation), only 13% were held by non-radiologists independently. Starting from 2019 31% of the studies are conducted by non-radiologists.

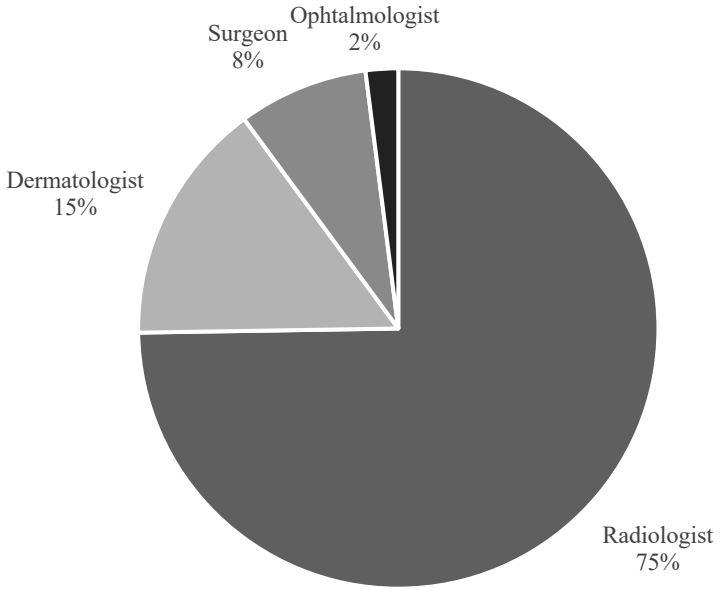

Figure 8. Operators’ specialization in included studies.

Velthuis et al [16], [17] describing US technique in their study, mark out main aspects for proper use of US equipment and result interpretation: the knowledge of US transducer

positioning and principles of facial orientation, the ability to recognize the different structures on US image. Study [17] also provides description of standard US transducer positions in the face. Two studies [15], [26] highlight importance of sonographic parameters knowledge for identifying and reporting injectable fillers.

Calomeni et al [76]and Cotofana et al [64] suggest that absence of direct skin contact is important for compression avoidance of tissues and vessels during US examination on the face, providing their studies applying transducer into the visualization gel, without skin contact or pressure.

Several studies [2], [15], [21], [26], [14], [59] focus on importance of correct interpretation and description of US patterns of different injectable fillers. Schelke et al [15] report 10 sonographic parameters for monitoring and describing fillers: echogenicity, texture, border, shape, diameter, quantity, internal characteristics, artifacts, anatomical location, evolution. Examining terminology and parameters Schelke et al [15] in given study suggest, that results may serve dermatologists with US usage.

Studies focused on fillers patterns provide thorough sonographic descriptions of different injectables. The degree of brightness of a structure displayed on the US is called echogenicity, as echogenic means capable of producing echoes [21]. Kwon et al [47] note that different dermal fillers are recognizable with the help of US, as they present different patterns of echogenicity on US findings.

Schelke et al [21] and Wortsman et al [3] describe in their studies basic terms and US findings based on echogenicity regarding different fillers usage for aesthetics:

- Anechoic – appears black on US image, no echoes (no reflection of soundwaves). Feature of water, fluids, abscess.
- Hypoechoic – appears as varying shades of dark grey on US image. Minimum reflection, lower amount of echoes. Feature of glands, muscles, large nerves, fluid-filled structures, vessels, hyaluronic acid.
- Hyperechoic – appears as white, high reflection and echo-rich. Feature of bone and teeth, ligaments, fibrous tissue, calcium hydroxyapatite.

- Isoechoic – appears as light grey, moderate reflection, on US image looks similar to surrounding soft tissues, having similar echogenicity to a neighbouring structure. Feature of fat, subdermis, dermis.
- Shadowing – appears if the sound beam fails to pass through an object so only shadowing is seen behind. Feature of bone, gas, air, calcification.

The texture within the deposits may be homogeneous or heterogeneous: [15]

- Homogeneous – filler or structure appear on US image as uniform in echogenicity
- Heterogeneous - filler or structure appear on US image as combination of more than one echogenicity

Based on echogenicity fillers (or reaction in tissue) will be imaged according to its particular qualities [3]. Different fillers might have hydrophilic or hydrophobic characteristics. HA fillers are hydrophilic as they are able to bind water. As water content does not reflect US waves HA appears black (echogenic) or dark grey (hypoechoic) on US examination pictures [3], [15].

Schelke et al [15] describe in their study HA as „well-defined oval- or round-shaped anechoic homogenous deposits without any signs of internal echoes “. In another study Schelke et al [21] describe HA findings as „anechoic to hypoechoic lesions with distinct echogenic walls, having hydrophilic characteristics “. Urdiales-Galvez et al [26] report HA-fillers to produce immediately after treatment anechoic image, globular and poorly defined patterns, like liquid content. At least one month after treatment the same study report HA-fillers to show patterns similar to healthy skin or subcutis, indicating integration into tissue.

Di Santolo [53] report HA-fillers as „anechoic round structures (pseudocysts) impure formulations of HA or as pseudocysts with inner echoes (debris) and septa in mixed formulations of HA (with lidocaine) “. Wortsman et al [2] describe pure HA-fillers findings as „anechoic round structures (pseudocysts) “, and report to HA-fillers with lidocaine to present „pseudocysts with inner echoes and septa “.

There are two published articles on usage of doppler US in cosmetic medicine (guide) [16], [17]. This work focuses on translating cadaver anatomy on US image, suggesting that US Imaging may be helpful, for example, in avoiding intra-arterial filler injections and determining precise location of different anatomical structures, and that filler injections should be

performed under US guidance or after US examination, examples also provide that highlight the benefits of US imaging which are safety and aesthetic outcome improving.

5 Discussion

5.1 Key findings and result interpretation

The aim of given thesis was to explore the current state of US technology usage in aesthetic medicine in terms of HA injectables.

Study findings show that interest in US in aesthetic medicine has increased greatly in recent years. The finding was expected and suggests that US might be of great importance as in everyday aesthetic practice, as well as in research work, however, requires some additional research for legitimate usage. As US is widely implemented in many areas of medicine it might provide an extensive application in aesthetics for various purposes [15]. With an increase in the frequencies of the sensors (and an extended opportunities for precise visualization), US examinations came to aesthetic medicine, allowing to examine the skin (at higher frequencies) and deeper structures - subcutaneous fat, SMAS, deep fat packages (lower frequencies) [21].

More than 10 years ago, Shelke [21], Grippaudo [73] and then Wortsman [14], published articles on the use of US to obtain information about fillers in soft tissues of the face, but only today the use of US is becoming a part of routine in aesthetic practice. One of the first studies about US for filler evaluation originated from 2008 [22], by year 2019 there were 9 studies per year, in 2020 and 2021 there were 12 studies per year established, showing growth from year 2008. Issue emerging from these findings is that rapid growth of US usage and reporting started from 2019 and was growing, since first usage of Doppler US for aesthetics was reported in 2018. Doppler technology application in aesthetics opened the prospects for vascular complications prevention or management improvement. As vascular adverse effect appears to have the most unpleasant outcomes, the interest to their prevention is massive, that has been observed in research since 2019, when prevailing number of studies are focused on Doppler technology application investigation.

Appears, that to date US implementation is still not researched substantially in order to draw broad and solid conclusions and may reflect low importance or impact of research, but most likely the novelty and the niche position of the topic are the main reason. Also, the use of US began to be more widely studied, tried out for various applications; especially with the discovery of doppler usage. There is abundant space for further progress in analyzing US efficiency and effects HA acid fillers administration.

Next objective was to outline main types of US applied for aesthetics. In first study established in 2008 [22] the potential of high-frequency US (20Mhz) was highlighted for injectable filler performance assessment. In further research Di Santolo [53] suggests lower frequencies 5-17 MHz in B-mode for soft tissue and filler examination, recommending higher frequencies for very superficial skin assessment. The wide range of different parameters and methods used for different applications indicates a lack of consensus and clear guidelines and data on what the technical requirements for performing ultrasound are.

Starting from 2018 new standard of procedures becomes possible as Doppler US is proposed for vascular mapping by Schelke et al [3]. Later Duplex US is proclaimed [32] [13] as gold standard for filler treatment sonography. The use of Duplex US is widely promoted in the aesthetic medicine field [19] and recent articles highlight its advantages. Even though non-sponsored studies were included into given research, papers of some authors [3], [16], [17] may reflect some personal bias as authors appear to be pioneers in promoting Duplex US and multidisciplinary US usage in aesthetics.

Findings presented above give an overview of main types of US for aesthetics. It is likely that certain guidelines for choosing the right technologies and frequencies may be useful for new professionals in the field of US in aesthetics, but the procedure requires a deeper knowledge to ensure providing correct examinations and reliable result. Devices on the market (such as portable doppler or duplex, can be connected to smartphones [15]) for use in aesthetics already have the necessary settings [19] and do not require immersion in theory, however, understanding the technical features of using this method may help the specialist obtain more extensive and reliable information during the study.

One initial objective was to determine what are the main applications and indications for US in aesthetics. Findings of given study corroborate with the ideas of Gerber et al [8] and Schelke et al [12] who declare that cadaver or surgical anatomy, or any other anatomical instruction may vary and differ from individual anatomy and US imaging of the face structures might provide anatomical insights prior to safe injectable treatments**.** Detailed sonographic investigation [63], [64], [67], [70], [71] of face blood vessels with Doppler provide support to previous findings and report detailed location and demonstrate individual anatomical features of patients. Helps identify and control treatment outcomes in potentially dangerous areas on the face [64], [71], [69], [77], [70]. Risk of bias for given outcome is high and might overestimate the intervention effects, as might be essentially specific to different outcomes

within the study and may not apply to the study as a whole or different situation. Wang et al [79] confirms this observation and conclude it their study, that Doppler US might be useful in many situations, it is important acknowledge that false negative result is possible, as sensitivity of US examination is easily affected by many factors, such as operator qualities and skills, and machine settings and modalities. In support of this argument Di Santolo [53] claims that to perform trustworthy US results sonography expert involvement is needed. Velthuis et al [16] suggest that medical professionals from any discipline can be trained to use US properly, remarking that vascular surgeons also implemented us into their practice and use it successfully.

Even though US seems like a promising technique for safety increasing there has been insufficient analysis of limitations and possibility of false negativity, whereas different apparatus, modalities, factory settings might affect sensitivity of examination [79]. Also, this technique is very operator dependent, proper training and knowledge are crucial to interpret the result and for differentiation, if examination is provided by non-radiologist. What is not clear yet, that even when radiologist provide the examination, is how they are supposed to recognize different fillers (even different HA), or how to report the problems with fillers [15], [14], [26]. Specific instructions are needed.

Reflection on fillers identification and detection are provided in three studies [2], [14], [26], presenting detailed description of findings included into the study, explaining patterns characterization and diagnoses. Though, given papers describe the evaluation of cutaneous or subcutaneous process they provided in the study, without instructions for readers. Schelke et al [15] comes out with the paper describing thoroughly ten potential findings that might be detected in aesthetics, proposing nomenclature standardization and reporting proposal for US findings. However, there is no evidence, that all fillers for all patients will generate only those findings, which can affect diagnosing for non-professionals. Though, recommendations and knowledge Schelke et al [15] present for examination and terminology might provide educative value for new-beginners, or for those who have to communicate with sonography experts. Currently, referring patients to US examinations from aesthetics, might be complicated and do not always provide expected assistance. This is primarily because imaging medicine physicians might not understand the features of aesthetic correction performed [17], [53]. For effective cooperation and best outcomes for patients US aesthetic professionals might attend training for independent US usage or effective communication with radiologist, but it is important to

aknowledge, that the legitimate process of US application in aesthetics is not specified, and independent usage os US in aesthetic practice is not supported by clinical data.

Concerning evaluation of filler sonography without reference to operator's frailty, findings show [48], [53], [62], [73] that in more than 97,5% and up to 100% cases provided by radiologists it was possible to assess and identify fillers with sonography, this finding further support the affirmation of Wortsman [14] that sonography is the first-choice imaging modality for detection, identification, and complication management of injectable fillers. The finding was expected and suggests that there is great potential for post-injection complication management improvement, when US can provide information of exact composition of the filler and its location, if needed, for dissolving manipulations. These findings may help to understand that, that multidisciplinary partnership should be provided for the best outcome for the patient in aesthetic medicine clinic, if it would be possible to engage radiologist for consultation and proper patient examination in case of emergency.

The next objective was to evaluate the usefulness of US technology implementation into aesthetics. Wortsman [14] suggests that" to date, sonography is the first-line imaging modality for dealing with cosmetic fillers". Similarly, other studies [13], [16], [17], [18], [54] report US technology as a gold-standard for injectable treatments in aesthetics. The data provided in those studies supports these arguments, all results report positive outcomes. However, it is important to reflect on credibility of such statements. For sure there is no need to argue about ability of US to visualise soft tissues in the face, but it still remains uncertain if the claim about US improving safety of fillers usage must be considered with accuracy, because research quality in given field is insufficient and does not provide evidence for supporting this statement.

The usefulness of US technology was evaluated in given research for diagnosis, management and treatment of complications as a safety enhancement method. Surprisingly, US usage was found to **have no support data or provement** that US application improves safety in aesthetics. The finding was unexpected and suggests that there is a need for large-cohort study to obtain relevant results to assess the outcome [22]. This finding corroborates the ideas of Young et al [20] who reported positive outcome of their study, where complication treatment was provided for patients (n=13) and satisfactory outcomes were achieved for all patients with Doppler. Young et al [20] acknowledge that large-scale studies are required to confirm any case series study findings.

However, it is important to note that it is pre-procedural US that has unproven efficacy in terms of improving safety. The ability to detect and identify the most common types of fillers [31], [49], their location, depth, and size [47], implies, that at current state US may be considered as the main technique for dealing with injectable fillers and late complications [49], as US appears to be proven and convenient non-invasive method for soft tissue examination, and is a r**ecognized method for the assessment of filler performance in soft tissue**, due to fillers ability to generate different patterns that are recognizable by US [26]. Given fact is not new [26] and implies, that US may be suggested as an efficient method for detecting, identifying, and managing late filler complications.

US for aesthetics is a soft tissue visualization technique that provides information but **doesn't improve safety by itself**. US does not protect from or prevent complication, but allows to visualize the anatomy or material location, for assessment. In general, obtained data from given study present US usage advantages, and even though there is no reliable scientific provement, yet that US improves safety, given state-of-the-art review collects and present data in favour of its appropriate usage.

The use of US is described to have many advantages, including: anatomical structures real-time visualization possibility, in situation of anatomical peculiarities; the ability to determine exact location and depth of blood vessels for vascular complication avoidance; precise injection of hyaluronidase for complication treatment; identification and detection of previously placed fillers, the spread and composition of them; evaluation and determination of filler complication; and complication management efficiency improvement [53], [74].

According to findings, main US **advantages and influence on injectable** fillers treatments outcomes may be **mainly post-procedural** and allow to monitor the changes caused by HA fillers or detect and evaluate potential adverse reactions caused with filler treatments. US proven ability for examining the skin or underlying tissues, and therefore to provide information about previously placed fillers or patient individual anatomy is also significant assent into aesthetic practice, that need to be researched and developed (guidelines) further.

If the incidence of complications in aesthetics continues to rise, more attention needs to be directed to their prevention. The real problem may not lie in the overall frequency of complications, but in the consequences for the patient that aesthetic procedures should ideally never lead to, especially now that tools are available to prevent and eliminate possible

complications. If the frequency of such complication grows, it may be necessary to involve government agencies to regulate the sector. It is likely that in the future we will conclude that the injection of dermal filler without help of imaging will not be possible and that, eventually, US will most likely become the standard of care. The author suggests that it is only a matter of time when US (probably portable) can be found in medical aesthetic clinics and the patient will need to undergo an US imaging of the face in order to perform the procedures.

The last objective was to provide main requirements for **trustworthy outcome**. Velthuis et al [16] note that most practitioners in aesthetic medicine may not be familiar with US usage and suggest that training about US examination process and findings interpretation may improve the knowledge gap and become more implemented into routine aesthetic practice. However, di Santolo [53] suggest that experts with sonographic knowledge should provide US examination, though not mentioning, what speciality is required. Appears, that even though US usage is highly promoted [16], [17] for multidisciplinary usage, Schelke et al [15] remark that utilization of new applications and interpreting US findings might be confusing for aestheticians with different backgrounds and specialities.

Appears, that HA filler findings may be described a bit differently by various authors, though mainly they match [2], [15], [21], [26], [53]. There may be several possible explanations for such a result, such as different fillers, apparatus, interval between injection and examination [26]. Another possible explanation for this might be the ability of operator to describe and interpret the findings, and knowledge of the meaning of different findings. Implication of these findings is the potential for further investigation and development of basic requirements for aesthetic sonography.

Findings of given study imply, that that many aspects must be considered in order to provide accurate US examination. To determine the location, depth, size and nature of the filler, knowledge of terminology is required, as well as the ability to interpret findings, read US images and draw parallels with various types of aesthetic treatments and possible complications. The ability to carry out the procedure technically appropriately, without discrediting the result, is crucial for reliable outcome.

It appears to be not specified, what are the requirements for legitimate process of US implementation into aesthetics, as given topic is very innovative and developing area in aesthetic medicine [15]. A further study with more focus on knowledge and skills should be

done to investigate operators' expertise concerns and main requirements for conducting proper US examination in aesthetics.

To date, appears that the scientific research regarding application of US for aesthetics is still not sufficient for evidence-based recommendations and guidelines.

The main requirements, emerging from findings [15], [16], [17], for providing proper US examination and obtain reliable results appear to be:

- the knowledge of US transducer positioning and principles of facial orientation
- the ability to recognize and identify different structures on US image
- importance of sonographic parameters knowledge for identifying and reporting injectable fillers
- ability to interpret and identificate patterns of different injectable fillers on US image

One of the main issues emerging from findings is operator-dependency and US application knowledge for providing a reliable result of the US assessment. The findings of the given study show, that majority of state-of-the-art research is carried out with the help of radiologists (75%), however, the findings of given study show that non-radiologist involvement into US usage has been growing by 113% in last 3 years. It seems likely that these results are in fact due to increased need for safety improvement [6], [30], [7] and promotion of US usage as potential complication prevention tool [3], [13], [19], [54].

The concept of US application might often seem misunderstood for non-radiologists, due to a lack of basic knowledge and limited training opportunities. Furthermore, the finding of the current study show, that information amount and quality in research papers concerning US technical knowledge is not able to provide reliable insights before sonography implementation into practice for proper understanding.

There are surprisingly few [3], [17], [21], [53] comments in published articles on the topic of expertise, only Di Santolo [53] suggest that radiologists must provide US examination. These findings differ from Velthuis [17] and Schelke et al [3], [21] who claim that any aesthetic medicine professional should implement US usage into their practice. This discrepancy could be attributed to Velthuis and Schelke involvement into portative doppler device training group [19], and even though they declare that they have no conflicts of interest or funding in their studies, contradictions in two findings and opinions raise questions if any opinion is biased.

From another point of view, perhaps US usage training experience for non-radiologists [19], encouraged doctors to promote US usage for aesthetic professionals (dermatologists, dentists, nurses, plastic surgeons etc.), as participants showed the ability to learn the US application basics for aesthetics.

Overall majority of included papers offer exceptional analytical and informative guide to the concepts of US applications. Several instructions are provided for how to provide examinations or interpret results, read findings, and maintain safe practice.

Despite the effort and time required to work effectively with sonographic imaging, it is a tool that may improve the safety of an injectable filler and aid in the diagnosis and treatment of adverse events, if provided appropriately. Patient safety, specialist calmness and composure, and the ability to diagnose, treat and probably prevent complications are all strong and important arguments for using US in aesthetic work.

The findings may help to emphasize, that it is not the technology that needs to be improved for aesthetics, but the knowledge of its application in aesthetics. Thereby, to some extent, study might contribute to the further improvement of the quality of injection procedures in the field of aesthetics.

5.2 Limitations

As a method, state-of the-art intend to review most up-to-date information and outline development and advancements in the given field of interest, thus all studies including case reports were included due to importance of every detail of information and proposed innovation or observation. This is considered as a limitation because case studies do not provide quality assessment and usually, they are associated with increased risk of bias.

Study limitations may exist due to constraints on research design, methodology, conflict of interest and personal bias, these factors can impact the findings of the study. Also, it should be mentioned, that in different studies examinations were not performed with the same device, but different devices and modalities were used. And also, the lack of reproducibility studies, among different operators. In other words, the reporting quality is the main issue with included studies and which applies main limitations on the quality of research evidence and should be aknowledged. Considering that reporting quality seems as a main problem different method

which requires and focuses on quality assessment might be considered for future research, especially if it aims to achieve more precise effect of the results.

Thus, as main limitation of given study is the absence of formal quality assessment because critical appraisal would allow to evaluate the quality of the research evidence which would provide reliable outcome of the research. Critical appraisal is necessary for informed decisions about the quality of scientific evidence.

Authors personal bias were reduced during research process and getting new information and data from sources. Also, findings were reviewed and discussed with peers. Measures as checking on objectives, following the research plan, were applied in order not to compromise or affect reliability and trustworthiness of the study.

Limitation as insufficient amount of patients examined should be considered separately, as some aesthetic complications (from HA fillers) are very rare, and studies still can provide interesting experience or highlight influential aspect. Important to acknowledge that outcomes of these studies may be influenced by the knowledge and skills of the providers, and therefore study results may be considered at risk of bias, to eliminate this factor, studies with blinded operators should be searched for and evaluated.

Given study includes only peer-reviewed articles from scientific journals, though the main designs of the studies are prospective and retrospective, which might have some limitations and factors that need to be considered if such an occasional event is being researched as complication in aesthetics. The word „occasional“ is consciously used here, because complication events are rare [70] and, for example, selection bias in retrospective studies may not discover problematic cases that provide correct and valid outcome. In terms of prospective studies, the follow-up period may not be sufficient and differential loss (to follow up) can lead to bias. Nevertheless, prospective studies provide outcomes concerning US advantages for post-procedural follow up monitoring, showing the ability of US to assess changes in tissues and the localization of fillers after treatment.

Literature analysis showed a limited number of clinical studies on representative samples or large-scale studies on the use of US, which does not allow to confidently extend the application of the results to the general population/general technology application. Therefore, another important limitation is, that there is no support data or provement to provide that US application improves safety in aesthetics. Studies are also provided by trained and engaged professionals,

other operators with no experience or proper knowledge in sonography or aesthetics, might interpret the results differently. In other words, „in a real world “, findings may not be applicable.

5.3 Recommendations

In a context of aesthetic medicine practice findings could provide state-of-the-art insights about safety improvement prospects, highlighting important aspects about injectable treatments outcomes enhancement and personnel competencies.

Further research based on methodology including proper quality assessment would provide reliable scientific evidence on US usage, strong enough for evidence-based authority for further application of US into aesthetics.

In aesthetics, US is a newly implemented application and evidence-based recommendations, and proper guidelines are very needed, as interest grows towards US usage. Given subject meet the need that future studies focus on exploring the considerations that aesthetic treatments providers should acknowledge before US imaging implementation into their practice, such as apparatus selection, training, US findings interpretation.

Hence, further additional research is needed to confirm whether US appear and might be handled as a safety improving method. A further study with more focus on operator abilities might help to investigate outcomes of US assessment of trained non-radiologists compared with experts’ performance. Appears, that to date US implementation is still not researched substantially in order to draw broad and solid conclusions and may reflect low importance or impact of research, but most likely the novelty and the niche position of the topic are the main reason. Also, the use of US began to be more widely studied, tried out for various applications; especially with the discovery of doppler usage. There is abundant space for further progress in analyzing US efficiency and effects HA acid fillers administration.

Supporting several suggestions described above, large-scale study is required, to provide greater statistical reliability regarding US usage outcomes in aesthetics. And also in the focus of guideline creating, it would be interesting to investigate the ability and progress of different medical professionals in US usage learning and the effect of post-graduate US training .

There is a clear need to further investigate the process and outcomes of US detection of complications, US guided injections and US anatomy investigation before treatment. Serious complications from fillers are rare and often delayed [9], but always extremely unpleasant, as for fillers healthy patient is being treated (without need for medical treatment) and patient's expectation is always for positive outcome. Due to rare incidence sometimes it's difficult to provide a study including large number of patients (fortunately) and focusing on one or two patients, but larger clinical studies might be needed to provide relevant and reliable results concerning US usage efficacy. Several authors have drawn attention to the fact that they present limited data and large-scale studies are required to confirm present data, hypotheses and development in the field [20], [22], [48], [55].

6 Conclusion

Aim was achieved and extend state-of-the-art present the current overview about the possibilities for application and the usefulness of US implementation into aesthetic practice. All research questions have been answered and point out that pre-procedural US allows to visualise blood vessels and post-procedural US may help to detect adverse reactions, though for reliable outcome operators' expertise is very important.

Given study set out to determine whether applying US into aesthetic practices has implications on HA injectables usage. US diagnostics of the face opens new prospects in aesthetics, implementation of US diagnostics into routine practice might improve safety outcomes of HA injectables in aesthetic medicine field. To date, appears that the scientific literature regarding application of US for aesthetics is still not sufficient for evidence-based recommendations and guidelines.

Most of the objectives of the research have been accomplished. Despite the novelty of the method for aesthetic medicine field, the research shows that US implementation practice is developing, finding more and more applications in aesthetics, many possibilities of US are being explored from different angles in order to improve injectable treatments outcomes. Only one research question remains insufficiently reported in the literature: at the moment studies seem to be focused on verification and justification of US implementation into aesthetics, and proper requirements for legitimate process and reliable result appear to be insufficient and undeveloped. However, given study highlights the main aspects and knowledge requirements that need to be acknowledged by new users.

In the conducted observations, the diagnostic value of US in aesthetic medicine was investigated. US is an objective research method allowing to examine the structure of the skin and deeper tissues and operate with the quantitative results of the assessment necessary to comply with the principle of evidence. Comparison of the results of US and the clinical picture increases the reliability of the data obtained during the examination. This method might be recommended for use in the treatment and diagnostic process for verification and control of injectable treatment outcomes, and evaluation of the effectiveness of treatment, as well as for the examination of the quality of medical services provided. The main directions of using US diagnostics in aesthetics are determining the normal anatomy, evaluating the effectiveness of therapy, preliminary examination, and control after the introduction of injectables.

To provide correct US examination and obtain reliable results- essential knowledge of accurate use of the device and the ability to interpret sonographic findings are crucial. The most reliable at the moment can be considered a study conducted by a radiologist, for the multidisciplinary application of ultrasound, training is required, as well as regulation for the usage and implementation of this method in aesthetic practice.

Considering the dynamic development of the use of US in aesthetic medicine, a promising direction of scientific research is to clarify the role of US in improving the safety of procedures, determining the information content of diagnostic criteria, and developing methods for predicting and monitoring the effectiveness of treatment.

Despite the effort and time required to work effectively with US imaging, it is a tool that can improve the safety of an injectable filler and aid in the diagnosis and treatment of adverse events. Patient safety, specialist peace of mind, and the ability to diagnose, treat and probably prevent complications are all strong and important arguments for implementing US into aesthetic practice.

Given study does not perform formal quality assessment of included studies, however critical appraisal of 3 aspects was provided to assess the quality of scientific evidence.

One of the main issues emerging from findings is operator-dependency and lack of interdisciplinary consensus regarding the implementation of US for providing a reliable result of the US assessment. Given finding might potentially be a problem for further approach of US technology, until training opportunities are enhanced and technology application standards for aesthetics are developed. The author's opinion in this regard is that clinics and aesthetic treatments providers should cooperate with radiologists to guarantee reliable results of US examinations. To improve interdisciplinary communication, all employees involved in aesthetic procedures at different stages should be trained and have extensive knowledge to interpret the results and communicate effectively. Coordinated interdisciplinary communication and teamwork of all professionals involved in sonographic examination in aesthetics might provide the best possible interpretation and outcome of US examination.

Despite improvements in technology and the emergence of more convenient and compelling US apparatus on the market, some difficulties remain against the full application of US in the practice of aesthetic medicine. Learning how to use US requires a lot of effort, time, and dedication from the specialist. It is also impossible to compete with sonography professionals.

The effectiveness of US depends on the operator, who needs skill and constant practice to become well versed in its use.

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Appendix 1 List of included studies

Authors	Title	Year	Publication	Measurement tool if appliable	Source
Mespreuve et al.	Visualization Techniques of the Facial Arteries	2021	Journal of Cosmetic Dermatology	N/A	PubMed
Mlosek et al.	The Use of High-Frequency Ultrasonography for the Diagnosis of Palpable Nodules after the Administration of Dermal Fillers.	2021	Journal of Ultrasonography	EPIQ 5, PHILIPS, Bothell, USA - up to 18MHz	PubMed
Rocha et al.	Description of a safe doppler ultrasound-guided technique for hyaluronic acid filler in the face-A method to avoid adverse vascular events.	2021	Journal of Cosmetic Dermatology	18mhz transducer	PubMed
Rocha et al.	Ultrasonography for long-term evaluation of hyaluronic acid filler in the face: A technical report of 180 days of follow-up.	2020	Imaging Science in Dentistry	8MHz, Vscan with Dual Probe;	PubMed
Lee et al.	Use of handheld ultrasound Doppler to prevent complications from intra-arterial injection of dermal fillers: Clinical experience.	2019	Journal of cosmetic dermatology	2MHz doppler Bidop ES-100V3	Embase
Turlier et al.	Assessment of the clinical efficacy of a hyaluronic acid-based deep wrinkle filler using new instrumental methods.	2010	Journal of Cosmetic and Laser Therapy:	20MHz Dermcup;	PubMed
Young et al.	Use of high-frequency ultrasound in the assessment of injectable dermal fillers. (54)	2008	Skin research and technology:	20 MHz, Episcan,	PubMed
Grippaudo et al.	High-frequency sonography of temporary and permanent dermal fillers.	2010	Skin research and technology	10-13 MHz Hitachi H21	PubMed
Schelke et al.	Early ultrasound for diagnosis and treatment of vascular adverse events with hyaluronic acid fillers. (40)	2019	Journal of the American Academy of Dermatology	Duplex US	ScienceDirect
Urdiales-Gálvez et al.	Ultrasound patterns of different dermal filler materials used in aesthetics.	2021	Journal of Cosmetic Dermatology	Samsung HT 30 a 12 MHz; General Electric Logiq S8; Logiq E with 18 MHz linear probe	PubMed

Pérez-Pérez et al.	Delayed Adverse Subcutaneous Reaction to a New Family of Hyaluronic Acid Dermal Fillers With Clinical, Ultrasound, and Histologic Correlation.	2017	Dermatologic Surgery:	Logiq E9 XD clear, linear probes 15 MHz and 18 MHz;	PubMed
Kwon et al.	The Utility of Color Doppler Ultrasound to Explore Vascular Complications After Filler Injection.	2019	Dermatologic Surgery:	Doppler US	PubMed
Velthuis et al.	A Guide to Doppler Ultrasound Analysis of the Face in Cosmetic Medicine. Part 1: Standard Positions. Part 2: Vascular Mapping	2021	Aesthetic Surgery Journal	N/A	PubMed
Schelke et al.	Use of ultrasound to provide overall information on facial fillers and surrounding tissue. Dermatol Surg.	2010	Dermatologic Surgery:	13MHz LOGIQ e B-mode, Linear Probe 12L-RS, GE Healthcare, Chalfont St. Giles, UK	PubMed
Wortsman et al.	Ultrasound detection and identification of cosmetic fillers in the skin.	2011	Journal of the European Academy of Dermatology and Venereology	7-15 MHz HDI 5000; Philips Medical Systems, Bothell, WA, USA	PubMed
Grippaudo et al.	The utility of high-frequency ultrasound in dermal filler evaluation.	2011	Annals of Plastic Surgery	10-13 MHz Hitachi H21 (Hitachi Medical Corporation, Tokyo, Japan)	PubMed
Huang et al.	Two-step, imaging-device–guided, precise filler-injection technique	2019	Journal of the American Academy of Dermatology	Acuson X150 , Siemens Medical Solution USA, Mountain View, CA	ScienceDirect
Jaguś et al.	Usefulness of Doppler sonography in aesthetic medicine.	2021	Journal of Ultrasonography	Philips Epiq 5 with 18–5 MHz linear transducer, Samsung RS85 with linear 4–18 MHz and L 3–12 MHz	PubMed
Bondarenko et al.	Sonography of the face and neck region soft tissues in assessment of the complications causes after facial contouring	2021	Georgian Medical News	10to22Mhz and 15to18Mhz, B-mode and Doppler	PubMed
Schelke et al.	Nomenclature proposal for the sonographic description and reporting of soft tissue fillers.	2020	Journal of Cosmetic Dermatology	N/A	PubMed

Scotto et al.	Clinical value of high-resolution (5-17 MHz) echo-color Doppler (ECD) for identifying filling materials and assessment of damage or complications in aesthetic medicine/surgery.	2019	La Radiologia Medica	Doppler 5-17mhz	PubMed
Lee et al.	Laser Doppler Imaging for Treating Vascular Complications from Procedures Involving Dermal Fillers: Case Series and Literature Review.	2021	Diagnostics (Basel, Switzerland)	MoorLDI2-IR; Moor Instruments, Axminster, UK	PubMed
Tansatit et al.	Ultrasound evaluation of arterial anastomosis of the forehead	2018	Journal of cosmetic dermatology	Doppler US	Embase
Mlosek et al.	High frequency ultrasound imaging as a "potential" way of evaluation modality in side effects of lip augmentation – case report	2018	Journal of Cosmetic and Laser Therapy	15MHz Philips EPIQ 5	PubMed
Cotofana et al.	Anatomy of the Superior and Inferior Labial Arteries Revised: An Ultrasound Investigation and Implication for Lip Volumization	2020	Aesthetic Surgery Journal	18 MHz LOGIQ S7 Expert, GE Healthcare GmbH, Solingen, Germany	PubMed
Huang et al.	Color Doppler Flow Imaging of Retrobulbar Ocular Blood Flow Changes in Retinal Artery Occlusions Caused by Cosmetic Facial Filler Injections	2018	Ophthalmic Plastic and Reconstructive Surgery	7,5 mhz Philips HDI 5000	PubMed
Teixeira et al.	Doppler ultrasound-guided volumizing of the glabella: a safe and effective method	2020	Journal of the American Academy of Dermatology	16 MHz Doppler	ScienceDirect
Lima et al.	External vascular compression by hyaluronic acid filler documented with high-frequency ultrasound	2019	Journal of Cosmetic Dermatology	10-22 MHz LOGIQ e (GE Healthcare)	PubMed
Goh et al.	Hyaluronic Acid Gel Distribution Pattern in Periocular Area With High-Resolution Ultrasound Imaging	2014	Aesthetic Surgery Journal	15MHz Logiq p6; GE Healthcare, Waukesha, Washington	PubMed
Qiao et al.	Long-Term Follow-Up of Longevity and Diffusion Pattern of Hyaluronic Acid in Nasolabial Fold Correction through High-Frequency Ultrasound	2019	Plastic and Reconstructive Surgery	20MHZ 3XSKIN; MEDA, Tianjin	PubMed
Calomeni et al.	Real-Time Ultrasound Imaging of the Tear Trough: Lessons Learned From Functional Anatomy	2021	Aesthetic Surgery Journal	L8-18 MHz Logiq e,	PubMed

Lee et al.	Safe Glabellar Wrinkle Correction With Soft Tissue Filler Using Doppler Ultrasound	2020	Aesthetic Surgery Journal	A two- dimensional Doppler ultrasound (E-cube 15ex model; Alpinion Co., Anyang, Korea) and a real-time color Doppler mode with a high-frequency (8–17 MHz) hockey-stick probe (I08- 17; Alpinion Co.)	PubMed
Cotofana et al.	The Change of Plane of the Supratrochlear and Supraorbital Arteries in the Forehead - An Ultrasound-Based Investigation	2020	Aesthetic Surgery Journal	18MHz Affiniti 70 Philips N.V., Amsterdam, Netherlands	PubMed
Schelke et al.	The mobility of the superficial and deep midfacial fat compartments: An ultrasound-based investigation	2021	Journal of cosmetic dermatology	18 MHz	Embase
Park et al.	Ultrasonography Analysis of Vessels Around the Forehead Midline	2020	Aesthetic Surgery Journal	ECUBE 15, Alpinion Medical Systems, Seoul, Korea. 8-15 MHz; IO8-17T, Alpinion Medical Systems	PubMed
Iwayama et al.	Ultrasonography-guided Cannula Method for Hyaluronic Acid Filler Injection with Evaluation using Laser Speckle Flowgraphy	2017	Plastic and Reconstructive Surgery. Global Open	N/A	PubMed
Moon et al.	Doppler Ultrasonographic Anatomy of the Midline Nasal Dorsum (34)	2020	Aesthetic Plastic Surgery	Doppler US	PubMed
Ten et al.	Evaluation of facial artery course variations and depth by Doppler ultrasonography	2020	Journal of Cosmetic Dermatology	14MHz Aplio 500; Toshiba Medical System Corporation, Tokyo, Japan	PubMed
De Pasquale et al.	Hyaluronic Acid Filler Injections for Tear-Trough Deformity: Injection Technique and High-Frequency Ultrasound Follow-up Evaluation	2013	Aesthetic Plastic Surgery	15MHz Accutome B-Scan Plus; Accutome, Inc., 3222 Phoenixville Pike, Malvern, PA, USA	PubMed
Lee et al.	Positional Relationship of Superior and Inferior Labial Artery by Ultrasonography Image Analysis for Safe Lip Augmentation Procedures	2019	Clinical anatomy (New York, N.Y.)	E-Cube 15, ALPINION with a B-mode high-frequency linear-array transducer 15 MHz; L8-17X,	Embase
Cotofana et al.	Relationship Between Vertical Glabellar Lines and the Supratrochlear and Supraorbital Arteries	2020	Aesthetic Surgery Journal	18 MHz LOGIQ S7 Expert,	PubMed

Urdiales-Gálvez et al.	Ultrasound assessment of tissue integration of the crosslinked hyaluronic acid filler VYC-25L in facial lower-third aesthetic treatment: A prospective multicenter study	2020	Journal of Cosmetic Dermatology	10 MHz linear array transducer ; 12 MHz linear array transducer	PubMed
Jaguś et al.	Usefulness of Doppler sonography in aesthetic medicine	2021	Journal of Ultrasonography	Philips Epiq 5 with a linear transducer and Samsung RS85 with linear transducers and Doppler Microflow Imaging option	PubMed
Wortsman	Identification and Complications of Cosmetic Fillers: Sonography First	2014	Journal of Ultrasound in Medicine:	LOGIQ E9 8 to18 and 5 to16 MHz,	PubMed
Schelke et al.	Ultrasound to improve the safety of hyaluronic acid filler treatments	2018	Journal of Cosmetic Dermatology	N/A	PubMed
Habib et al.	Management of Dermal Filler (Vascular) Complications Using Duplex Ultrasound	2020	Dermatologic Therapy	12 MHz, Duplex	PubMed

Appendix 2 Impact score and h-index of all Journals of included papers

Journal	Impact score	h-index
Aesthetic Surgery Journal	1,87	58
Journal of Cosmetic Dermatology	2,36	44
Skin research and technology: official journal of International Society for Bioengineering and the Skin	1,90	69
Aesthetic Plastic Surgery	1,48	67
Journal of Ultrasonography	0,77	3
Dermatologic Therapy	1,48	68
Plastic and Reconstructive Surgery	2,16	179
Journal of the American Academy of Dermatology	3,49	208
Dermatologic Surgery: Official Publication for American Society for Dermatologic Surgery	1,19	125
Journal of the European Academy of Dermatology and Venereology: JEADV	2,57	107
Journal of Cosmetic and Laser Therapy: Official Publication of the European Society for Laser Dermatology	1,72	50
La Radiologia Medica	3,04	47
Imaging Science in Dentistry	1,81	22
Annals of Plastic Surgery	1,16	91
Journal of Ultrasound in Medicine: Official Journal of the American Institute of Ultrasound in Medicine	1,92	91
Journal of the German Society of Dermatology: JDDG	0,79	60
Clinical anatomy	1,94	71
Ophthalmic Plastic and Reconstructive Surgery	1,05	56
Diagnostics	3,24	19
Georgian Medical News	0,25	15