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Review

Evaluating the quality of studies reporting on clinical applications of stromal vascular fraction: A systematic review and proposed reporting guidelines (CLINIC-STRA-SVF)

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ABSTRACT

Background: The stromal vascular fraction (SVF) has been widely explored in a number of therapeutic applications in several specialties. Its therapeutic potential is being increasingly demonstrated, although its mechanism of action is still unclear.
Objective: To evaluate the quality of studies reporting on clinical applications of SVF.
Method: This is a systematic literature review that followed the PRISMA guidelines with the search of the studies from December 1, 2012, to December 1, 2022, in the following databases: MEDLINE, LILACS and EMBASE. The level of evidence of the studies was assessed using the GRADE system, and the rigor used in the publication of the results was assessed in relation to adherence to the guidelines indicated by the EQUATOR Network Group. The CLINIC – STRA-SVF reporting guideline was developed after the completion of this systematic review.
Results: A total of 538 articles were found, and 77 articles were selected after reading the titles and abstracts and removing duplicates. Then, 15 studies were removed for not meeting the inclusion criteria, leaving 62 studies. The CLINIC – STRA-SVF was developed and consists of 33 items and two tables.
Conclusion: There is scientific evidence, although mostly with a low level of evidence, that the use of SVF in clinical applications is safe and effective. The information published in these studies should be standardized, and the CLINIC – STRA-SVF reporting guideline proposed in this study may assist in the design, conduct, recording and reporting of clinical trials and others clinical studies involving the SVF.

Contents

Abbreviations: ADSCs, adipose tissue stem cells; VEGF, vascular endothelial growth factor; HGF, hepatocytic growth factor; PDGFB, platelet-derived growth factor subunit B; bFGF, basic fibroblast growth factor; SVF, stromal vascular fraction; BM-MSCs, bone marrow-derived stem cells; EPCs, endothelial progenitor cells; CLINIC–STRA-SVF, Strengthening Reporting in Therapeutic Applications of the Stromal Vascular Fraction Guideline; FDA, United States Food and Drug Administration; AEs, Adverse events.

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1. Introduction

One of the most important characteristics of adipose tissue, in addition to its thermoregulation, impact absorption and energy storage, is that it is a source of regenerative cells [1]. In 1893, Neuber et al. removed fat from the forearm and used it to fill in volume and correct irregularities in the contour of the face caused by a scar, and reported excellent cosmetic results [2]. Two decades later, Morrestin was the first to clinically and beneficially apply regenerative adipose tissue cells by transferring adipose tissue particles to the wounds of soldiers injured in World War I [3]. Since then, fat has been increasingly investigated, and hundreds of studies have been published. Today, the scientific medical community continues to develop, modify, refine and innovate techniques for exploiting the potential of adipose tissue [4].

In 2001, Zuk et al. demonstrated *in vitro* that populations of cells isolated from adipose tissue obtained by liposuction can differentiate into adipocytes, chondrocytes, osteocytes and myocytes [1]. Today, it is known that in addition to this ability, adipose tissue stem cells (ADSCs), have antiapoptotic [5], antioxidant, anti-inflammatory and immunomodulatory properties [6].

These cells also exhibit angiogenic function, through the regulation of the expression of vascular endothelial growth factor (VEGF), hepatocytic growth factor (HGF), platelet-derived growth factor subunit B (PDGFB) and basic fibroblast growth factor (bFGF) genes [7] and may also aid wound healing by stimulating collagen synthesis by fibroblasts [8].

Through the processing of fat, which can be enzymatic or mechanical, it is possible to obtain the stromal vascular fraction (SVF), which is a rich source of ADSCs [9]. In addition, the SVF represents a convenient source of ADSCs because it is easily obtained and yields a higher proportion of stem cells than other methods of isolating mesenchymal stem cells [9]. The field of application of ADSCs is greater than that of bone marrow-derived stem cells (BM-MSCs) in regenerative medicine, due to their greater availability and because they involve an easier isolation technique than BM-MSCs [10]. In addition, 1 g of fat contains 1000 times more stem cells than 1 g of bone marrow, and the quality and proliferation capacity of these cells do not decrease with age [1,12].

The SVF includes cells of the immune system, especially T helper lymphocytes, pericytes, fibroblasts, endothelial cells and stromal precursor cells [13,14]. The two main stem cell phenotypes present in SVF are endothelial progenitor cells (EPCs) and ADSCs; the main actions of SVF are pro-angiogenic, anti-apoptotic, antifibrotic, immunomodulatory, anti-inflammatory and trophic. Some of these actions can be attributed to the presence of ADSCs (2–10%), while others are associated with the vascular niche, and, alternatively, the interactions between all cellular phenotypes present in SVF together with the various growth factors [15].

The SVF is an important source of blood vessel-associated cellular phenotypes, including pericytes (adventitial location), endothelial progenitors (luminal location), mesenchymal progenitors, supra-adventitial adipose stromal cells (vessel sheath), and endothelial cells [16].

The SVF has been widely explored by various medical specialties in various clinical situations. Because its use is a promising possibility for clinical applications, there is a need to investigate all clinical studies, compare them and understand the benefits of the SVF to formulate appropriate protocols for its use. The objective of the present study was to evaluate the quality of studies reporting on clinical applications of SVF.

2. Methods

The present study is a systematic literature review performed in the Medline, Lilacs, and Embase databases following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17], therefore complying with the Enhancing the Quality and Transparency Of health Research (EQUATOR) guidelines [18], covering studies published in the period from January 12, 2012 to January 12, 2022, in Portuguese, Spanish and/or English.

In the Medline database, the following search strategy was used: ("stromal vascular fraction" *[MeSH Terms]*) AND ("clinical application" OR "wound healing" *[MeSH Terms]* OR burn OR "face rejuvenation" OR cicatrix *[MeSH Terms]* OR therapeutics *[MeSH Terms]* OR "cardiovascular diseases" *[MeSH Terms]* OR "musculoskeletal diseases" *[MeSH Terms]* OR "respiratory tract diseases" *[MeSH Terms]* OR "female urogenital diseases" *[MeSH Terms]* OR "male urogenital diseases" *[MeSH Terms]* OR "Eye Diseases" *[MeSH Terms]* OR "regenerative medicine" *[MeSH Terms]* OR "autoimmune diseases" *[MeSH Terms]* OR "neurodegenerative diseases" *[MeSH Terms]* OR "pressure ulcer" *[MeSH Terms]* OR "plantar fat pad atrophy").

The following was used in the Embase database: 'stromal vascular fraction' and 'clinical application'. And the following was used in the Lilacs database: "stromal vascular fraction".

Studies were included if they were clinical trials, prospective and retrospective cohorts, case series and case reports, only in humans and that used enzymatically extracted stromal vascular fraction. We excluded experimental studies, secondary studies, studies that did not use freshly isolated SVF, studies that were retracted for ethical reasons, studies that used SVF extracted by ultrasound or mechanical cavitation, and studies that did not describe the method of SVF processing.

After reading the title and abstract, all retrieved articles were tabulated and included in a database. The selection and reading process of the articles were performed by two of the authors (MYF and JC). All articles selected by the two authors were definitively included in the systematic review. The articles selected by only one of the authors were analyzed by the senior author (LMF) and included only when there was agreement among the three authors. The full text was obtained for the full evaluation and final inclusion of the articles.

The level of evidence of the studies was classified by the authors according to the levels determined by the Grading Recommendations, Assessment, Development and Evaluations (GRADE) System [19]. The studies were evaluated regarding adherence to the EQUATOR Network Guidelines [18]; specifically, each type of study design was evaluated according to the appropriate guidelines: randomized clinical trials – CONSORT [20]; clinical trials – Guidelines for reporting non-randomised studies [21]; case studies series – PROCESS [22]; case reports – CARE [23], and observational studies – STROBE [24].

The studies were evaluated in relation to the methodology for evaluating the manifestations and monitoring of adverse events (AEs), following the recommendations of the study "Reporting Adverse Events in Plastic Surgery: A Systematic Review of Randomized Controlled Trials" [25].

The preparation of the CLINIC – STRA-SVF – Strengthening Reporting in Therapeutic Applications of the Stromal Vascular Fraction Guideline was performed following the AGREE [26] recommendations, in addition to "How to develop a reporting guideline" [27] of the EQUATOR Network [18], and was guided by the results obtained in the evaluation of the studies included in this review. Before starting the preparation of the Guideline, a search on the Equator Network [18] platform was performed to verify the existence of published or under development reporting guidelines applied to publications of clinical studies involving the stromal vascular fraction, through December 2022.

The data contained in the included articles were independently extracted by the researchers and evaluated together to obtain consensus on the information therein.

3. Results and discussion

In total, 538 articles were initially identified. Of these, 77 articles were selected after reading the titles and abstracts and removing duplicates. Then, 15 studies were removed because they met the exclusion criteria, leaving 62 studies [28–89]. (Fig. 1) After reading

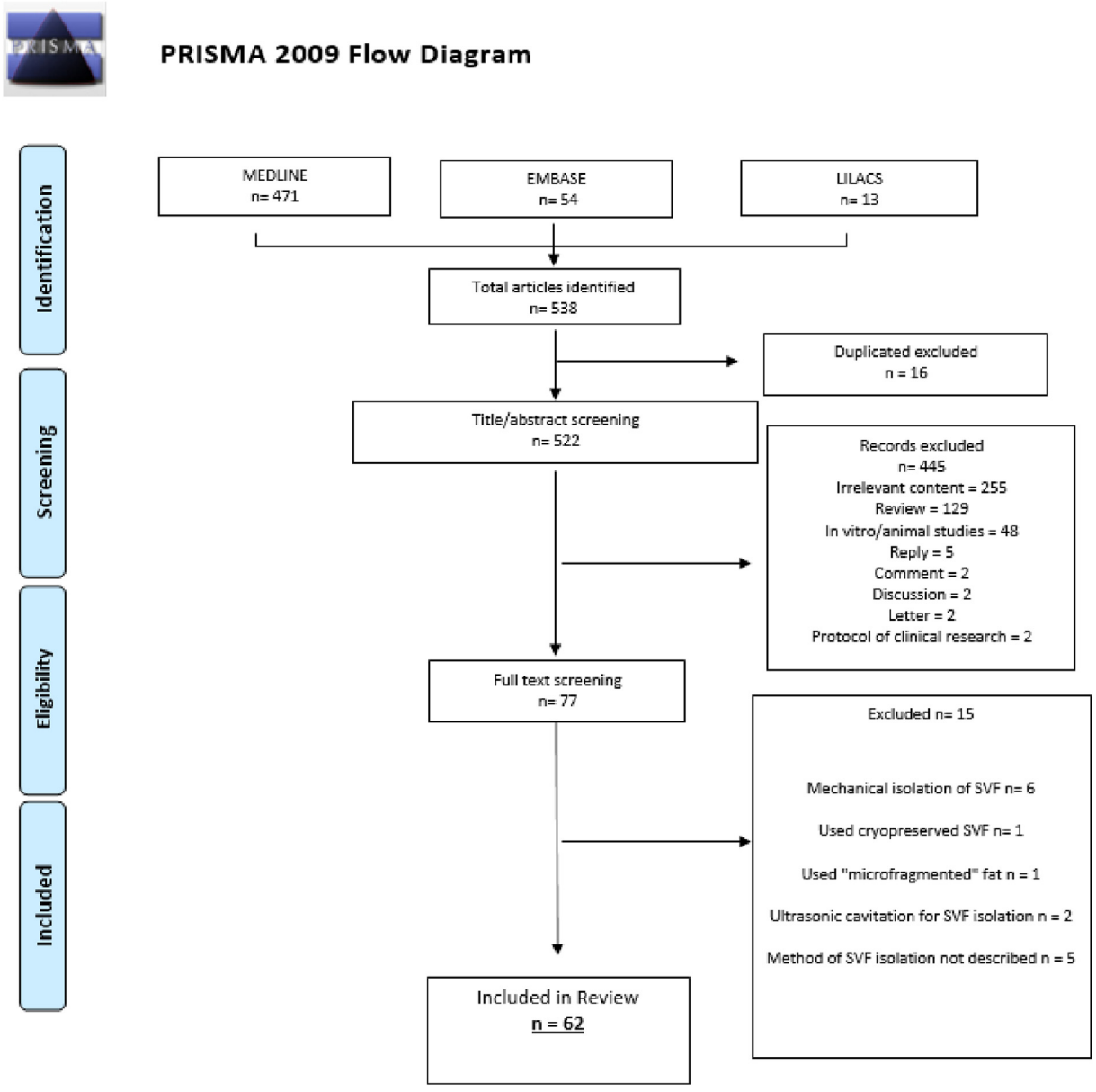

Fig. 1. Prisma flow diagram.

and completely analyzing these articles, all of them were included in the present review.

3.1. Therapeutic applications

A total of 41 different therapeutic applications were found in the selected studies, as shown in Table 1. The most prevalent therapeutic applications in the studies were osteoarthritis of the knee (n = 9; 14.5%) and volume restoration in breast reconstruction (n = 6; 9.7%). The identified studies showed that several specialties have a promising future in the use of SVF, especially in relation to pathologies in which the available treatments do not offer a cure. The therapeutic objectives ranged from the use of SVF for cosmetic/aesthetic purposes such as facial rejuvenation, which enhances aesthetic results in procedures involving fat grafting, to therapeutic procedures in osteoarticular, neurological, cardiovascular diseases and vocal cord injuries, infertility, neuromas, post-trauma and poststroke sequelae, autoimmune diseases (e.g., systemic sclerosis and ankylosing spondylitis), neurodegenerative diseases (e.g., Parkinson's and Alzheimer's), chronic and refractory fistulas and ulcers, erectile dysfunction, etc. (Table 1)

Table 1
Therapeutic applications.

	No. (%)
Therapeutic objective	
Osteoarthritis of the knee	9 (14,5%)
Volume restauration in breast reconstruction	6 (9,7%)
Perianal fistulas of Crohn's disease	3 (4,8%)
Systemic sclerosis	3 (4,8%)
Androgenetic Alopecia	2 (3,2%)
Atrophic acne scars	2 (3,2%)
Diabetic ulcer	2 (3,2%)
Peripheral vascular disease	2 (3,2%)
Alopecia areata	1 (1,6%)
Asherman's Syndr	1 (1,6%)
Avascular necrosis femoral head	1 (1,6%)
Bone regeneration	1 (1,6%)
Breast aumengtation	1 (1,6%)
Chondromalacia patellae	1 (1,6%)
Chronic fatigue and depression in Ankilosing Spondylitis	1 (1,6%)
Contracted nose – rev. rhinoplast	1 (1,6%)
Contracted scars	1 (1,6%)
Cosmetic and Recons approachs	1 (1,6%)
Cryptoglandular Fistulae-in-Ano	1 (1,6%)
Degenerative disc disease	1 (1,6%)
Erectile Disfunction	1 (1,6%)
Infraorbital Skin Rejuvenation	1 (1,6%)
Ischemic cardiopathy	1 (1,6%)
Lymphedema	1 (1,6%)
Neurodegenerative Disorders	1 (1,6%)
Nose after BCC excision	1 (1,6%)
Osteonecrosis of the jaw	1 (1,6%)
Orthopedic pathologies	1 (1,6%)
Painful neuroma	1 (1,6%)
Parkinson's disease	1 (1,6%)
Photoaging	1 (1,6%)
Posterior lumbar interbody fusion	1 (1,6%)
Rejuvenation	1 (1,6%)
Salvage of Ischemic Fasciocutaneous flap	1 (1,6%)
Scarred Vocal Folds	1 (1,6%)
Solid neoplasies	1 (1,6%)
Stroke rehabilitation	1 (1,6%)
Treatment of amputed site	1 (1,6%)
Treatment of ulcus cruris of venous/mixed venous arterial	1 (1,6%)
Urinary incontinence	1 (1,6%)
X ray injury	1 (1,6%)

Table 2
Authors reported benefits?

	No. (%)
Yes	56 (90,3%)
No	3 (4,8%)
Only safety	3 (4,8%)

3.2. Prevalence of studies that reported clinical benefits

The data extracted from the studies included in this review are encouraging regarding the use of SVF. Most studies reported statistically significant clinical benefits in the results (n = 56; 90.3%); 3 studies were designed to evaluate safety only [63,82,89], and the remaining 3 studies reported that the use of SVF did not offer benefits in improving pain in 5 cases of painful neuromas [59] or volume retention in breast reconstruction [53,77], although in the latter application, another study reported the efficacy [81] and another demonstrated the safety of SVFs [82]. (Table 2).

Although the mechanism of action of the SVF, in its various clinical applications and methods of application, is not yet fully understood, these studies demonstrate the therapeutic potential of the SVF.

3.3. Summary study details

The year of publication of the studies, the country where the study was conducted and the journal in which the article was published are shown in Table 3. The years with the highest number of published articles were 2020 (n = 13; 21%) and 2016 (n = 10; 16.1%), the countries with the highest number of published articles were South Korea (n = 12; 19.9%) and the USA (n = 11; 16.6%), and the journals with the largest number of published articles were Stem Cell Res Ther (n = 6; 9.6%) and Aesthet Surg J (n = 5; 8%).

3.4. Route of administration of the SVF

The most prevalent routes of administration in the included studies were subcutaneous (n = 16; 25.8%) and intra-articular (n = 15; 24.2%). Two intravenous applications were performed and demonstrated safety, with no reports of adverse effects [54,62]. Innovative forms of SVF application have been described, such as intramyocardial, intraventricular (brain), suburethral, intravocal folds, intracavernous, intratumoral, intrauterine and enriching dermis grafts (Table 4).

In this review, the therapeutic applications of the SVF were used alone and in combination (e.g., SVF + PRP - Platelet-Rich Plasma -, SVF + L-PRP - leukocyte- and platelet-rich plasma -), SVF + Fat Graft, SVF + ACAM2000); the routes were intravenous in a total of 26 patients, intraperitoneal in 4 patients, intratumoral in 17 patients, intracavernous in 17 patients, intramyocardial in 28 patients, intrauterine in 6 patients, and intracerebral in 31 patients (with a total of 113 applications were performed); among all of these, no serious adverse effects were reported during the follow-up. One patient received intravenous application of a thawed SVF after cryopreservation, and with a 3-year follow-up, the study reported an absence of AEs. One patient received a combination of SVF + PRP that was frozen for 10 days for treatment of a refractory foot ulcer that remained unhealed for 2 years, and the study reported treatment efficacy and the absence of AEs.

Table 3
Summary details of the 62 studies.

	No. (%)
Year of publication	
2022	6 (9,6%)
2021	5 (8%)
2020	13 (21%)
2019	5 (8%)
2018	9 (14,5%)
2017	6 (9,6%)
2016	10 (16,1%)
2015	5 (8%)
2014	1 (1,6%)
2013	1 (1,6%)
Country	
South Korea	12 (19,3%)
USA	11 (17,7%)
France	7 (11,3%)
China	5 (8%)
Nicaragua	4 (6,4%)
Belgium	2 (3,2%)
Brazil	2 (3,2%)
Denmark	2 (3,2%)
Germany	2 (3,2%)
Iran	2 (3,2%)
Australia	1 (1,6%)
Greece	1 (1,6%)
Italy	1 (1,6%)
Japan	1 (1,6%)
Lebanon	1 (1,6%)
Pakistan	1 (1,6%)
Poland	1 (1,6%)
Spain	1 (1,6%)
Switzerland	1 (1,6%)
Taiwan	1 (1,6%)
The Neterlands	1 (1,6%)
Thailand	1 (1,6%)
Vietnam	1 (1,6%)
Journal	
Stem Cell Res Ther	6 (9,6%)
Aesthet Surg J	5 (8%)
J Cosmet Dermatol	3 (4,8%)
J Transl Med	3 (4,8%)
Stem Cells Transl Med	3 (4,8%)
Aesth Plast Surg	2 (3,2%)
Ann Plast Surg	2 (3,2%)
BMC Musculoskelet Disord	2 (3,2%)
Cells	2 (3,2%)
Plast Reconstr Surg	2 (3,2%)
Stem Cell Res	2 (3,2%)
Surg Innov	1 (1,6%)
Adv Clin Exp Med	1 (1,6%)
Am J Sports Med	1 (1,6%)
Ann Rheum Dis	1 (1,6%)
Biomed Res Int	1 (1,6%)
Curr Res Transl Med	1 (1,6%)
EBioMedicine	1 (1,6%)
Eur J Obstet Gynecol Reprod Biol	1 (1,6%)
Eur Rev Med Pharmacol Sci	1 (1,6%)
Gastroenterology	1 (1,6%)
Health Phys	1 (1,6%)
Int J Low Extrem Wounds	1 (1,6%)
Int Orthop	1 (1,6%)
J Clin Neurosci	1 (1,6%)
J Eur Acad Dermatol Venereol	1 (1,6%)
J Int Med Res	1 (1,6%)
J Med Case Rep	1 (1,6%)
J Orthop Surg Res	1 (1,6%)
J Plast Reconstr Aesthet Surg	1 (1,6%)
J Stomatol Oral Maxillofac Surg	1 (1,6%)
JAMA Otolaryngo Head Neck Sur	1 (1,6%)
Medicine (Baltimore)	1 (1,6%)
Microsurgery	1 (1,6%)
Mol Biol Rep	1 (1,6%)
PLoS One	1 (1,6%)
Regen Med	1 (1,6%)
Reprod Sci	1 (1,6%)
Rheumatology (Oxford)	1 (1,6%)
Stem Cells Int	1 (1,6%)
Surg Cosmet Dermatol	1 (1,6%)

Table 4
Route of administration.

	No. (%)
Subcutaneous	16 (25,8%)
Intra-articular	15 (24,2%)
Intradermic	7 (11,3%)
Injected in the wound	5 (8%)
Peri/intra-fistular	4 (6,45%)
Between muscles	2 (3,2%)
Engineered dermis graft	1 (1,6%)
Into the corpo cavernosum	1 (1,6%)
Intradiscal	1 (1,6%)
Intralesional (contracted nose)	1 (1,6%)
Intramiocardic	1 (1,6%)
Intramuscular	1 (1,6%)
Intrauterine	1 (1,6%)
Intravenous	1 (1,6%)
Intravenous and/or intra-tumoral and/or intra-peritoneal	1 (1,6%)
Intraventricular (brain)	1 (1,6%)
Intra-vocal folds	1 (1,6%)
Peri-fascial and peri-chondral	1 (1,6%)
Suburethral	1 (1,6%)

In all these applications, the safety of the applications was reported, although at different levels of evidence, providing more confidence for the scientific community to establish new trials that demand such applications.

3.5. Design, methodological rigor and level of evidence of the studies

Only 6 (9.7%) of the studies were randomized clinical trials, and 26 (41.4%) were nonrandomized clinical trials, demonstrating that approximately 50% of the studies included in this review were case series, case reports, and cohorts (Table 5). These data demonstrate the low quality of the available evidence because without robust and randomized studies, the evidence obtained will always be limited or have a low level of confidence. This low level of confidence was also the result obtained in the application of the Grade System [20] classification on the included studies, which resulted in 56 (90.3%) articles with a low level of evidence and 6 (9.68%) articles with a high level of evidence.

The EQUATOR Network [16] is an initiative recognized and endorsed by scientific medical journals worldwide. The platform provides guidelines, materials and tools that offer solutions necessary for studies to be prepared and published with the maximum scientific rigor possible by the medical community and an extensive list of guidelines that can be used in each design and/or study area. The group is defined as “an ‘umbrella’ organization that brings together researchers, medical journal editors, peer reviewers, developers of reporting guidelines, research funding bodies and other collaborators with mutual interest in improving the quality of research publications and of research itself” [18]. The data extracted from the studies regarding adherence to the

Table 5
Methodological details of the studies.

	No. (%)
Design of the study	
Randomized clinical trial	6 (9,7%)
Non-randomized clinical trial	26 (41,4%)
Case series	9 (14,5%)
Case report	10 (16,1%)
Case-Control	1 (1,6%)
Retrospective Cohort	3 (4,8%)
Prospective Cohort	7 (11,3%)
EQUATOR network recommen-dations	
Yes	3 (4,8%)
No	59 (95,2%)
GRADE classification	
Low	56 (90,3%)
High	6 (9,68%)
Adoppted EQUATOR recommedend guideline	
None	59 (95,2%)
CONSORT	1 (1,6%)
Nonrandomized guideline	0 (0%)
PROCESS	0 (0%)
CARE	0 (0%)
STROBE	2 (1,6%)
Other guidelines adopted	
GPP – Guidelines 2022 [90]	1 (1,6%)
AIOM - follow-up guidelines [91]	1 (1,6%)
ICH-GCP [92]	2 (1,6%)

Table 7
Details about adverse events (AEs).

	No. (%)
A validated method to access AE was used?	
No	59 (95,16%)
Yes	3 (4,8%)
Anticipated AE clearly defined	
No	55 (88,7%)
Yes	7 (11,3%)
Was it clear who would be documenting any AE?	
No	62 (100%)
Yes	0 (%)
Ocurrence of AE reported?	
No	42 (67,74%)
Yes	20 (32,26%)
Authors declared that AE reported was common and no serious AE of the type of the proccedure and/or not related direct to SVF	17 (85% of 20)
Statement saying there where or no AE?	
No	17 (27,4%)
Yes	45 (72,6%)
Total number of AE that authors declared that there was a proba-ble relationship with SVF	3 (4,8%)
Neoplasy transformation reported	0 (0%)
Method for access AE	3 (4,8%)
CTCAE	1
MOSES	1
MedDRA	1

EQUATOR guidelines and the guidelines suggested by the group show that almost none of the studies related to therapeutic applications adhered to these guidelines; only 3 of the 62 studies adhered to them, resulting in a 95.2% nonadherence rate. The three studies that adhered to the study used the CONSORT (n = 1; Mattei et al. [45]) and STROBE (n = 2; Moon KC et al. [50] and Lee JW et al. [58]) recommendations.

The results of the GRADE classification and the adherence of the studies to the EQUATOR guidelines demonstrate that the studies related to the clinical applications of SVF are of low quality.

3.6. Follow-up

The follow-up time, the description of the presence or absence of AEs, and the methodology used to assess the presence of AEs are determining factors in the publication of the safety of the new therapies studied. Regarding the follow-up, most studies involved a period between 12 and 36 months (n = 40; 64.5%), and the mean was 18.6 months (Table 6). The studies were accessed to extract data related to the methodology for evaluating the AEs according to previously published guidelines [25]. Among the 62 studies, 59 (95.16%) did not use a validated method to access and classify the AEs of the established therapies, and 55 (88.8%) did not define in advance which AEs would be evaluated during the follow-up. Furthermore, none of the 62 (100%) reported who the researcher or collaborator responsible for documenting the AEs was, and a total of 17 (27.4%) did not mention the presence or absence of AEs, which should be considered a fundamental error in studies that seek to describe clinical applications of new therapies (Table 7).

Tabela 6
Follow-up.

	No. (%)
<1 months	1 (1,6%)
1–5 months	4 (%)
6–11 months	14 (%)
12–23 months	25 (%)
24–36 months	15 (%)
More than 37 months	3 (%)

Of the 62 studies in this review, only 20 (32.26%) reported the presence of AEs, among which 17 studies declared that the AEs were somehow directly related to the type of intervention performed, such as surgical site infection, knee inflammation after intra-articular application, and pain resulting from liposuction. No serious adverse events, such as death, thromboembolic events, neoplastic transformations or hypersensitivity reactions that could generate a risk of death and/or hemodynamic instability or neurological changes related to the SVF were reported.

3.7. Details and scientific rigor applied in the evaluation of the AEs

Of the 62 studies, 59 (95.16%) did not use a validated method to assess the AEs of the established therapies, 55 (88.8%) did not define in advance which AEs would be evaluated during the follow-up, 62 (100%) did not report who the researcher or collaborator responsible for documenting the AEs was, 42 (67.74%) reported that there were no AEs and 20 (32.26%) reported AEs. Of the 20 authors who reported AEs, 17 (85% of the reported AEs) reported that the effects were related to the instituted procedure and not directly related to the SVF, and 3 (4.8% of all studies) reported that the AEs were directly related to the SVF. None of the authors reported neoplastic transformation during the follow-up of the studies, as shown in Table 7.

Among the studies, a total of 17 (27.4%) did not mention the presence or absence of AEs. The studies that used methods to evaluate AEs used the following guidelines/methods: MOSES [93], MedDRA [94] and the Common Terminology Criteria for Adverse Events (CTCAE) [95].

The lack of validated methodologies and the lack of publication of the methodology and the people involved in the evaluation of the AEs hinder the reproducibility of the studies, which may make the published evidence of safety questionable and incapable of demonstrating its reliability *per se* using the published methods.

As important as it is to describe the adverse events, it is also necessary that the authors adopt a method of identification, follow-up, classification and publication of these events and that they make this clear in the publication, ensuring that, from the study

protocol, the AEs are accessed according to previously published guidelines and following validated methods [25].

3.8. Details about the SVF: characterization, viability, total cells, and nomenclature used by the author

Of the 62 studies, 28 (45.16%) did not report the total nucleated cells in the SVF, 36 (58%) did not report the cell markers present in the SVF used, and 32 (51.61%) did not describe the viability of the SVF cells (Table 8). There are numerous variables that influence the viability and quantity of cells present in the SVF, and to compare doses, therapeutic effects, and adverse effects, it is necessary to know exactly which and how many cells were present in the SVF used and their corresponding viabilities.

Among the studies that published the markers of the cells present in the SVF, there was a great difference in the way they were published and in the number of markers that were evaluated. To allow a comparison and a better understanding of the SVF and its clinical applications, works that involve the SVF must evaluate and publish the markers of the cells present in a standardized manner as previously described [15,96,97].

More than 60% of the SVF cells is $CD34^{+}$, a marker present in the cells of the vascular niche. The composition of the SVF may vary depending on the processing protocol [98–100], and in the studies included, numerous protocols were used. The International Federation for Adipose Therapeutics (IFATS) and the International Society for Cellular Therapy (ISCT) have provided guidelines and recommendations for the minimum basic characterization of the SVF, i.e., $CD45^{-}CD235a\text{-}CD31^{-}CD34^{+}$ [97].

Regarding the nomenclature used by the authors to describe the stromal vascular fraction, a total of 7 different acronyms were used: SVF (n = 49; 79%), ADSVF (n = 7; 11.3%), AD-SVF (n = 1), ADSVCs (n = 1), ADRCs (n = 1), ASCs (n = 1) and ADSCs (n = 1) (Table 8). This difference in the use of acronyms to refer to the stromal vascular fraction makes standardization and better indexing of these articles, as well as future searches in databases, impossible, generating confusion that can and should be avoided. On January 01, 2022, the term “stromal vascular fraction” was indexed as a medical subject heading (MeSH) term and thus should be used in future clinical studies involving the use of SVF.

3.9. Studies with therapeutics with any relationship with oncological pathologies

An important concern in the context of the therapeutic applications of stem cells is the carcinogenic potential and the concern generated, especially in patients who have or had affected by neoplasms.

In this review, six of the included studies reported 184 oncological related patients who were exposed to SVF therapies [38,50,54,57,63,81], with a mean follow-up of 30.8 months and a range of 6–96 months. None of the studies reported neoplastic transformations and/or an increase in the number of relapses, thus reinforcing the safety of the use of SVF (Table 9). These studies are fundamental for the advancement of the application of SVF in new therapies, serving as a basis for demonstrating evidence on the safety of the SVF to regulatory agencies such as the FDA conferring safety for the physician and the patient who will be treated with such therapy.

3.10. CLINIC – STRA-SVF Guideline development

No reporting guidelines published or under development were identified on the EQUATOR platform with regard to studies involving the SVF.

At the conclusion of this systematic review, the CLINIC – STRA-SVF guideline was developed, producing a checklist with 33 items and two tables that includes the fundamental information that should be published in studies evaluating therapies related to SVF (Tables 10–12).

The guideline was developed with the intention of being applicable to the complete elaboration of a study, from the writing of the initial project and research protocol to the execution during the follow-up, and through the publication of the collected information.

The present study investigated the clinical scope and the quality of studies reporting the use of enzymatic-extracted stromal vascular fraction in clinical application, through the level of evidence of the publications, the methodologies used to perform the research and publish the results, the quality of the information related to the SVF, as well as the results obtained in these studies and the safety of the use of the SVF in these applications. In an era where regenerative medicine and cell therapies have emerged promising therapeutic solutions for various pathologies and regenerative applications, the worldwide medical-scientific community has begun to increasingly exploit the potential of ADSCs and a worldwide dedication to investigating the relationship between the fat, the stromal vascular fraction and its regenerative potential in a wide range of preclinical and clinical studies in an expanding

Table 8
Details about SVF.

	No. (%)
Was reported the total nucleated cells in SVF?	
No	28 (45,16%)
Yes	34 (54,84%)
Was reported the markers of cells present in SVF?	
No	36 (58,06%)
Yes	26 (41,94%)
Was reported the viability of SVF cells?	
No	32 (51,61%)
Yes	30 (48,39%)
Nomenclature used for SVF	
SVF	49 (79,03%)
ADSVF	7 (11,3%)
AD-SVF	1 (1,6%)
ADSVCs	1 (1,6%)
ADRCs	1 (1,6%)
ASCs	1 (1,6%)
ADSCs	2 (3,2%)

Table 9
Oncologic related studies.

	No. (%)
Total patients exposed to SVF therapeutic	184
Medium follow-up	30,8 months
Range follow-up	6–96 months
Jeon HJ et al. [39]	
N;=	20
Follow – up	12
Moon KC et al. [51]	
N;=	77 (30 SVF group)
Follow-up	35 months/range - 1-8y
Minev BR et al. [55]	
N;=	26
Follow-up	6 months
Calabrese et al. [58]	
N;=	169 (41 SVF)
Follow - up	At least 60 months
Mazur S et al. [64]	
N;=	298 (56 SVF)
Follow-up	36 months
Tissiani LAL and Alonso N [82].	
N;=	19 (11 SVF group)
Follow-up	36 months

Table 10
CLINIC – STRA-SVF checklist.

Section	Item	Checklist Item
Study Design	1a	Study conducted in accordance with EQUATOR network guidelines?
	1b	CONSORT (RCT), Guidelines for Reporting non-randomised studies (NRCT), STROBE (cohort, case-control or cross-sectional), PROCESS (case series) or CARE (case report)
	1c	Validated method was used to access Adverse Events?
	1d	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)
Therapeutic objective	2a	Clear description of the therapeutic goal
	2b	Clear description if it's the first study in that scope or all previous studies published
	2c	Clear description about the outcomes that will be evaluated
General details	3a	Objective description of the method of the outcome assessment (Validated tools, assessment method proposed by the author and the reason it was chosen)
	3b	Description of the age and gender of the patients
	3c	Exact description of the fat harvest site
	3d	Complete description of the fat processing method (specifying whether it was extracted manually or by an automated method. What device was used.)
	3e	Detailed description of the enzyme and concentration used for enzymatic digestion
	3f	Description of the amount of fat harvested, amount of fat processed by the enzymatic process, amount of SVF obtained, and ratio of SVF yield/mL of fat processed.
	3g	Description of the time interval between fat collection, start and end of enzymatic processing
	3h	Description regarding the form of SVF used: immediately after processing cryopreserved other manipulations (describe which manipulation was done)
	3i	The nomenclature used was SVF - Stromal Vascular Fraction?
SVF Charac-terization	4a	Description of the SVF characteristics according to Table 12
	4b	Description of the characterization of the cells according to the markers
	4c	Characterization of the cells present in SVF by the markers
Application Details	5a	Description of the application method with number of applications
	5b	Description of the applied quantity and/or combination used
	5c	Description of the interval time between fat collection and application of SVF
Pos-op	6a	Description of dressing used
	6b	Description of post-procedure care/orientations
Follow-up	7a	Description of the patients follow-up time
	7b	Description of the interval and number of evaluations performed during the patients' follow-up
Adverse events (AEs)	8a	What validated method was used to access AEs?
	8b	How was classified the severity of the AEs?
	8c	The patients were informed about the possible and probable AEs?
	8d	Description of the evolution of the AEs and how it was treated
Outcome Results	9a	Objective description of the results
Funding	10a	Sources of funding and other support (such as supply of devices or drugs, products related with SVF), role of funders

global market [4,101–109]. This can be explained by its greater availability and ease of extraction or its higher cell yield relative to other forms of stem cell extraction [9–11]; thus, SVF has become the focus of attention, discussion and investigation by both clinical and surgical specialties. However, the literature is still recent, and publications on clinical applications are not standardized and still lack the necessary scientific rigor. This lack of standardization makes reliable comparisons impossible, and thus, a systematic review can aid in this regard by demonstrating the current scientific evidence regarding the use, risks, efficacy, safety and other peculiarities involved in the various possibilities of the application of the SVF. Thus, in this panorama, the key aspects that will enable progress in the methodological standardization of future publications on the clinical applications of SVF are emphasized.

3.11. Present, future, needs and encouraging highlights

The applications found in the articles included in this study, their results and safety, confer legitimacy to the establishment of new therapeutic hypotheses and deepening our understanding of the investigations already conducted. The use of the SVF for the benefit of patients, especially for diseases for which we currently do not have well-established effective therapies such as neurodegenerative diseases (e.g., Parkinson's, Alzheimer's, Multiple Sclerosis), autoimmune diseases (e.g., scleroderma, ankylosing spondylitis), heart diseases involving areas of tissue necrosis, erectile dysfunction and many others, is encouraging, opening the possibility for new studies to test new applications and further exploring the regenerative, immunomodulatory and anti-inflammatory potential of SVF.

Table 11
Model for evaluation and reporting the characteristics of stromal vascular fraction.

Stromal Vascular Fraction	Mean/range
Adipose Tissue Harversted (cm [3])	
Volume isolated (ml)	
Number of viable nucleated cells (VNC) (millions) obtained	
Recovery rate (VNC/cm [3] adipose tissue)	
Number of VNC injected or applied (millions)	
Viability (%)	

New studies involving the clinical applications of the SVF should focus on increasing the scientific rigor of investigations and publication of results, providing the necessary reproducibility, greater transparency and level of confidence in the published evidence [110–112].

In summary, it was evident that there was a lack of standardization in publications and basic information related to SVF, including the techniques used for collection, extraction, and application, patient follow-up, and other factors. This lack of standardization hinders the availability of consistent information and limits the ability to make comparisons and produce stronger scientific evidence. Some studies, did not publish information such as the age of the patients or the location of fat collection, which is basic information for this type of study. As concluded by Kelley et al. [113], “unless the data are comparable and the original studies are of high-quality, meta-analysis should be avoided in favor of a comprehensive systematic review. Inappropriate pooling of data should be avoided to preserve the quality of the research and to

Table 12
Model for evaluation and reporting markers of the SVF cells.

Subpopulation	Marker	(%)
Hematopoietic cells	CD45+	
Monocytes	CD45+/CD14+/CD206-	
Macrophages	CD45+/CD14+/CD206+	
Progenitor Endothelial Cells	CD45-/CD34+/CD31+	
Pericytes	CD45-/CD34-/CD146+	
Supra-adventitial stromal cells	CD45-/CD34+/CD31-	
Early mesenchymal stem cells	CD45-/CD34+/CD73+/CD90+	

avoid unjustifiable conclusions. Adherence to the principles of the scientific methods outlined will improve publication acceptance rates and the overall quality of literature in the field." This is also a concept that should be taken into account in the acquisition of robust scientific evidence related to the SVF.

In addition to this context, the reproducibility of the studies must be guaranteed by the author during the project preparation period, during the research and at the time of publication of the results. Corroborating the findings of Ascha et al. [111], this study demonstrates that research reproducibility is a mandatory component of the scientific method and is necessary for ensuring the accuracy of the scientific findings and for cultivating transparency and reproducibility in scientific research.

In this context, the authors of this review, driven by the evident need for standardization as observed during the preparation of this systematic review, proposed the creation of the CLINIC – STRA-SVF Guideline. The checklist aims to be easy to apply, and the authors encourage researchers to prepare their research projects and protocols using the guideline for the development of a highly scientifically rigorous method. At the time of publication, the authors should seek to fill in as many items in the guideline as possible according to the reality and possibilities of their research projects to ensure transparency, reproducibility, standardization and progress in the construction of evidence related to the clinical applications of the SVF.

Randomized clinical trials and prospective cohort studies, both highly rigorous in methodological design, in the publication of results and detailed information, and validated methodologies for evaluating the adverse effects of the clinical applications of SVF should be encouraged, following the CLINIC – STRA-SVF guideline recommendations in the reporting of these studies.

3.12. Study limitations

Although this systematic review was prepared following the PRISMA guidelines and sought through the EQUATOR guidelines and the GRADE system to infer the level of evidence and identify the global state of the clinical applications of SVF, it was difficult to compare the information due to the low level of rigor in the methodological approaches and the lack of standardization, reproducibility and transparency of the included studies.

4. Conclusion

There is scientific evidence of the safety and effectiveness in the clinical application of the SVF; however, the level of evidence of most of the studies was low, and much of the evidence was published in articles that do not follow the reporting methods used by the scientific community worldwide and that do not use validated methodologies for the evaluation of adverse effects. It is necessary to standardize the information published in the studies involving therapies with SVF, and the CLINIC – STRA-SVF reporting guideline proposed in this study may assist in the design, conduct, recording and reporting of clinical trials, case series, and case reports involving the SVF. The use of the CLINIC – STRA-SVF guideline will ensure the construction of studies and the publication of evidence that guarantee the reproducibility, comparisons and transparency necessary for future scientifically rigorous comparisons to be performed by the world scientific community and thus the construction and accumulation of better evidence for the benefit of patients.

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Declaration of competing interest

None.

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